RELISTOR® (METHYLNALTREXONE BROMIDE) FOR THE TREATMENT OF OPIOID INDUCED CONSTIPATION

NDA 021964 (APPROVED 2008)
sNDA 021964/S-010 (COMPLETE RESPONSE LETTER July 27, 2012)

BRIEFING DOCUMENT FOR THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE MEETING OF 11-12 JUNE 2014

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1.0 EXECUTIVE SUMMARY

This briefing document has been prepared by Salix Pharmaceuticals, Inc. (Salix), a specialty gastrointestinal (GI) pharmaceutical company dedicated to developing drugs in areas of unmet medical need that significantly impact patient lives. This document provides background information on Relistor® (methylnaltrexone bromide or MNTX) for the June 11-12, 2014 Anesthetic and Analgesic Drug Products Advisory Committee meeting. Contained in this briefing document is a summary of the nonclinical, clinical, and post-marketing data as it relates to cardiovascular (CV) adverse events with Relistor.

There remains an unmet need for an effective treatment for opioid-induced constipation (OIC) in patients taking opioids for chronic non-cancer pain (NCP). OIC is a serious and often intolerable side effect of opioid therapy. Over-the-counter laxatives and other currently available treatments are often ineffective. Patients who fail or cannot tolerate currently available therapies are faced with reducing or stopping their pain medication in order to have a bowel movement or continuing with the additional pain and discomfort associated with the constipation.

Relistor® subcutaneous (SC) injection, a peripherally acting mu opioid receptor antagonist, is currently approved and available for OIC in 31 countries and has never been removed from any country due to safety reasons. In the United States (U.S.), Relistor has been available since 2008 for the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. The usual schedule is one dose every other day as needed (see current Relistor® prescribing information in Appendix 10.1).

Following the approval in advanced illness, development programs were conducted for SC Relistor and an oral Relistor tablet formulation for the treatment of OIC in NCP patients. In 2011, a supplemental New Drug Application (sNDA) was submitted to the Food and Drug Administration (FDA) for a label expansion of SC Relistor to the NCP population. The sNDA was supported by the totality of Relistor data from > 150 nonclinical studies, 65 clinical studies (phases 1-4), and extensive worldwide postmarketing use. Relistor has a receptor targeted mechanism of action and physiochemical properties that restrict blood-brain barrier penetration, thereby sparing the central analgesic effects of opioids (1;2). Studies demonstrate that Relistor has favorable tolerability and a rapid onset of action that is maintained regardless of the amount or type of opioid the patient is taking. Unique to Relistor is the ability to dose on an as needed (PRN) basis with no evident attenuation of efficacy over time.

Following completion of the review of the Relistor SC sNDA for NCP, Salix received a Complete Response Letter (CRL) from the review Division at the FDA. The issues raised were concerns over a potential class effect based on an imbalance in CV events seen in a single study conducted with a different mu opioid receptor antagonist, and the lack of a control group in the SC Relistor 48-week NCP safety trial (Study 3358) to allow for interpretation of CV events observed in the study. Based on these concerns, the FDA indicated that a large CV outcome trial (CVOT) would be required prior to approval. Salix appreciates the challenges of addressing potential CV safety issues for non-cardiac drugs and welcomes the opportunity to discuss the

nonclinical, clinical, and postmarketing data of Relistor as it relates to the potential class issue raised by the FDA.

1.1 Unmet Medical Need

Estimates indicate that > 40% of chronic pain patients on opioids experience OIC (3-8), and in contrast with other opioid side effects, tolerance to OIC does not develop over time (9;10). Patients with OIC suffer from a constellation of symptoms that diminish their quality of life (QoL) and ability to perform normal daily activities. These symptoms include abdominal pain, cramping, bloating, hard stools, straining, painful defecation, and an ongoing sense of incomplete evacuation. Illustrating OIC's impact, cancer patients with OIC have rated it as a more common source of distress than their cancer pain (11).

OIC frequently limits the utility of opioids in treating chronic pain (10). Many chronic pain patients with OIC alter or temporarily abandon their opioids, trading constipation relief for pain (12;13). Others increase their opioid dosage or rotate to a different opioid in response to increasing pain from OIC. Opioid dose escalation, dose changes, and frequent rotation of opioids increases the risks of prescribing error, patient dosing errors, opioid overdose, opioid-related death, and other serious opioid toxicities (14-20).

Existing therapies in chronic NCP patients do not address the underlying cause of OIC and are limited by poor efficacy, burdensome side effects, and unpredictable timing of laxation. Laxatives are the most frequently attempted therapy, however, their efficacy in OIC is unproven, they are often poorly tolerated, and they are associated with well-known side effects. A Cochrane review failed to demonstrate any benefit for laxatives in OIC (21;22). The only FDA approved drug for OIC in chronic NCP patients is Amitiza® (lubiprostone), a chloride channel activator (23). Clinical trials for Amitiza in OIC have demonstrated only a marginal benefit versus placebo (23), and the drug has many limitations, including a lack of demonstrated efficacy in patients on methadone, reduced efficacy with increasing opioid dose, and adverse reactions (e.g., dyspnea and nausea) which may result in discontinuation of therapy (see Section 2.3).

Constipation has not been definitively established as an independent risk factor for CV events. There appears to be only one study in the literature which cites severe constipation as a potential risk factor for serious CV events. The study identified severe constipation as a risk factor in a secondary analysis of this observational study (> 70,000 post-menopausal women) from the Women's Health Initiative (24). In a clinical setting, patients presenting with underlying CV disease and constipation with straining are often treated for their constipation in an attempt to reduce the hemodynamic changes associated with straining. Literature describes the CV effects of straining with constipation related to the Valsalva maneuver (i.e., holding one's breath and bearing down) while attempting to pass a bowel movement (25-29). This maneuver leads to a number of acute vascular changes including increased chest pressure, reduced coronary blood flow to the heart, decreases and increases in blood pressure, and changes in heart rate (25-29). Patients taking opioids for chronic pain who develop OIC often present with elevated straining scores. The availability of targeted and effective therapies to reduce the number and severity of straining episodes in this specific population is extremely limited.

1.2 Efficacy of Relistor for OIC in Patients with Chronic NCP

Efficacy data is available for SC Relistor in the treatment of OIC in patients with advanced illness (approved NDA) and NCP (sNDA under appeal), as well as for oral Relistor in the treatment of OIC in NCP (phase 3). Clinical studies across all development programs have shown that Relistor provides rapid and reproducible relief of OIC (Section 3.0). Relistor's efficacy profile includes: a receptor targeted mechanism of action; rapid onset of laxation (within hours); PRN administration; and efficacy regardless of the amount of morphine equivalents or type of opioid. The number needed to treat (NNT) for benefit ranges from 2.5 to 5. The current package insert contains the efficacy data for the indication of OIC in patients with advanced illness (Appendix 10.1).

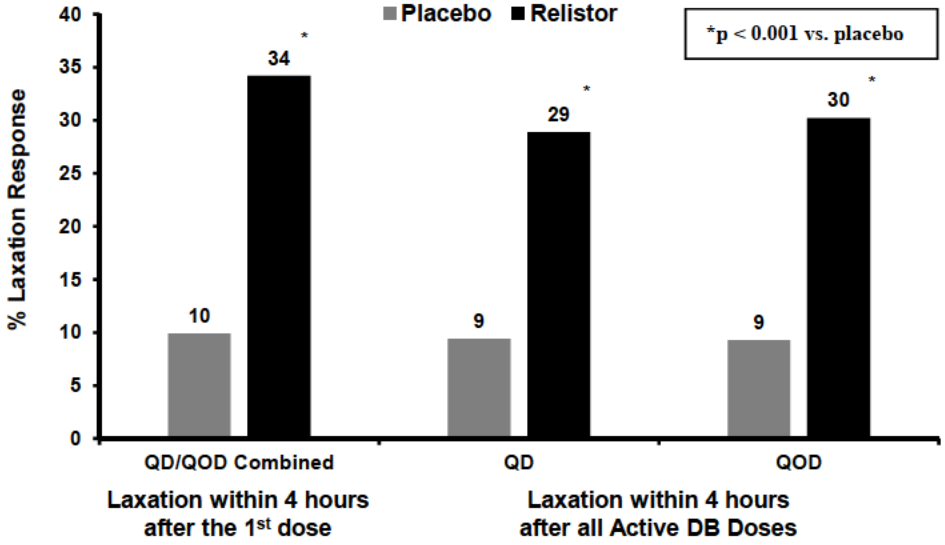
The sNDA for patients with NCP was based on results from two phase 3 studies:

- Study 3356 - a pivotal, randomized, placebo-controlled study of SC Relistor in 460 patients with NCP and OIC. The study included a 4-week, double-blind treatment phase followed by an 8-week, open-label Relistor treatment phase. There were 3 treatment groups during the 4-week, double-blind phase: Relistor 12mg once daily (QD); Relistor 12 mg once every other day (QOD); and placebo. The protocol called for two co-primary endpoints: the proportion of subjects having a rescue-free bowel movement (RFBM) within 4 hours of the first dose, and the percentage of active injections resulting in a RFBM within 4 hours during the double-blind period. During labeling discussions for SC Relistor for NCP, the Division of Gastroenterology and Inborn Errors Products (DGIEP) requested that another prospective endpoint be used which counts a responder as a patient that has ≥ 3 RFBMs per week during the 4-week double-blind period.
- Study 3358 - a 48-week, open-label safety study evaluating SC Relistor in 1,034 patients with NCP and OIC. Patients were instructed to take SC Relistor 12 mg QD, as needed. Patients were required to take at least 1 dose per week.

Relistor provides durable relief and an effect shortly after dosing for patients. Figure 1 summarizes results for the co-primary endpoints for Study 3356. Patients in the Relistor treatment groups had significantly higher rates of RFBMs within 4 hours of their first doses compared with placebo (34% vs. 10%; $p < 0.001$). Similarly, the percentages of all active injections resulting in a RFBM within 4 hours were significantly higher in the Relistor QD (29%; $p < 0.001$) and QOD (30%; $p < 0.001$) groups compared with the placebo group (9%). For the DGIEP-requested endpoint, significantly more patients who received Relistor 12 mg QD achieved ≥ 3 RFBMs per week versus placebo (59% vs. 38%, $p < 0.001$) during the double-blind period of Study 3356.

Patients receiving Relistor also demonstrated this durable response during 48 weeks of treatment in Study 3358. In the long-term trial, Relistor patients demonstrated significant improvements from baseline over the course of the study in weekly RFBMs, straining, stool consistency (Bristol Stool Scale), sense of complete evacuation, and QoL.

Figure 1: Study 3356: Co-Primary Efficacy Endpoint Results



Abbreviations: QD=once daily; and QOD=once every other day.
Note: P-values were based on a two-sided Chi-square test for the responses following the first dose and two-sided t-tests for the responses following all double-blind doses.

1.3 Regulatory History of the SC Relistor sNDA

The Relistor SC injection was initially approved by the FDA in 2008 for the treatment of OIC in patients with advanced illness. In 2011, a sNDA was submitted to the FDA requesting a label expansion for SC Relistor to include patients with NCP suffering from OIC. The clinical studies in the sNDA demonstrated a statistically significant and clinically meaningful benefit, with a safety profile consistent with the current Relistor prescribing information.

Upon completion of the sNDA review, the DGIEP issued a CRL. The issues raised in the CRL were concerns over a potential class effect based on an imbalance in CV events seen with a different mu opioid receptor antagonist in a 1-year, placebo-controlled trial (alvimopan; see Section 1.4) and the lack of a control group in the 48-week NCP safety trial for Relistor (Study 3358) to allow for interpretation of CV events observed in the study. In addition, the agency noted concerns about the potential for drugs in the pharmacologic class of opioid receptor antagonists to cause opioid withdrawal symptoms and suggested a potential link between the hemodynamic and autonomic nervous system effects of opioid withdrawal and CV events.

The CRL laid out the Division's request for a randomized, controlled, CVOT as the only acceptable means of evaluating the relative risk of major adverse cardiac events (MACE) prior to approval of the sNDA.

Following a number of interactions with the agency and the end-of-review meeting with DGIEP, Salix filed a formal appeal of the CRL decision to the FDA in April 2013. In response to the appeal, the FDA determined that an advisory committee would be the best means to address the issue of a potential CV class effect and to discuss the necessity, timing, design and size of

CVOTs to support approval of products in the class of opioid receptor antagonists for the treatment of OIC in patients with NCP.

1.4 Imbalance in Ischemic CV Events in a Study with Alvimopan

The FDA's concern regarding CV safety is based on data reported to FDA in 2006 from a single clinical trial of alvimopan in the treatment of OIC – Study GSK014. The 1-year, placebo-controlled trial with alvimopan showed imbalances versus placebo in the number of ischemic CV events and particularly myocardial infarctions (MIs) (30). DGIEP evaluated GSK014 during their review and subsequent approval of alvimopan (Entereg®) for POI in 2008 (31).

In Study GSK014 patients were allocated in a 2:1 ratio to receive either alvimopan 0.5 mg twice daily (BID) PO or matching placebo. The trial did not predefine a CV outcome committee and did not require complete capture of all safety data through 52 weeks regardless of subject withdrawal. Approximately 70% of patients enrolled in the study discontinued prior to the end of the study at Week 52. In total, 7 patients on alvimopan had a MI versus none on placebo. The relative risk (95% confidence interval [CI]) of having a MI in GSK014 was 7.46 (0.4, 130) on alvimopan versus placebo. The majority of MIs occurred within 90 days of first dose and none occurred after 111 days. When safety data from all non-cancer pain OIC trials for alvimopan were pooled, 8 of 1728 patients (0.5%) on alvimopan had an MI versus 2 of 790 patients (0.3%) on placebo. The overall relative risk of having a MI was 1.83 (0.4, 8.6) on alvimopan versus placebo (32).

The reason for the imbalance in CV events in GSK014 was never identified. The development of alvimopan for OIC was discontinued by the then product sponsor (GlaxoSmithKline) without an additional study conducted to determine whether the finding was a reliable signal or a chance occurrence. It was noted both by the FDA and the product sponsors at the time (GlaxoSmithKline and Adolor) that the imbalance in serious CV events was not observed in other alvimopan trials, including studies in POI and 2 placebo-controlled studies in OIC patients treated for 90 days (32). At the January 23, 2008 meeting of the Gastrointestinal Drugs Advisory Committee, the sponsor of alvimopan presented findings from an independent data monitoring committee that adjudicated CV events in the pooled alvimopan OIC studies. The committee concluded that the incidence of ischemic CV events was similar for alvimopan and placebo in the pooled analysis of OIC trials (32).

In the review of alvimopan for the POI indication, the FDA noted that the excess number of events was reported in only a single, long-term trial, and that it was possible that the finding occurred purely by chance (33). The FDA also concluded in their review that there was insufficient evidence in the literature to support a cardioprotective effect of opioids or cardiotoxic effect of opioid antagonists (33). Since this time, several papers have been published that estimate the relative risk of CV events in patients with chronic pain receiving opioids which suggest that while event rates are low there is an increased risk associated with chronic opioid use (14;15;34). The most robust of these studies was a claims-based study of ~150,000 adults on chronic opioid therapy reported by Carman et al. (see Section 6.3.2).

The potential CV signal in Study GSK014 has not been observed in short or long-term studies of any other peripheral opioid receptor antagonists. This includes the 48-week, open-label Relistor Study 3358 and a 52-week trial of naloxegol (35), another morphine-based peripheral mu opioid antagonist. In addition, clinical experience with approved opioid antagonists (Relistor, naltrexone, and naloxone) has not identified any apparent signal with respect to CV safety (33).

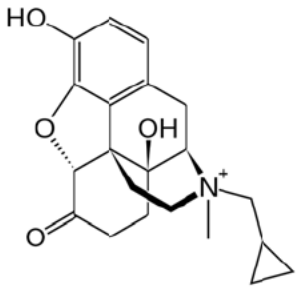
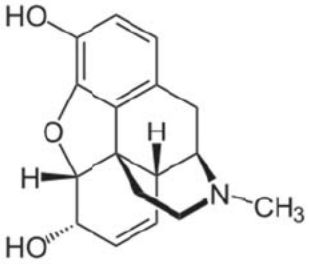
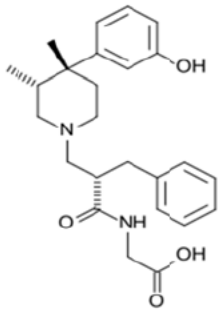
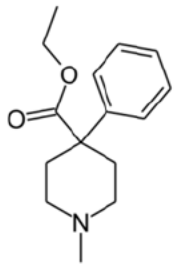
1.5 Nonclinical and Clinical Pharmacology of Opioid Receptor Antagonists

Nonclinical and clinical pharmacology data available from members of the peripheral mu opioid receptor antagonists class demonstrate differences in their physicochemical, pharmacological and dispositional (absorption, distribution, metabolism and excretion; ADME) characteristics. As a result, members of the class vary in how they are administered (oral vs. SC), frequency of administration (PRN vs. QD vs. twice daily [BID]), and efficacy.

Relistor's rapid and reproducible onset of action led to its current FDA- labeled indication for OIC in patients with advanced illness who are receiving palliative care, administered as a SC dose taken as 1 dose every other day, as needed, but no more frequently than 1 dose in a 24-hour period. This dosing regimen is consistent with the drug's pharmacokinetics (PK) and pharmacodynamics (PD); its efficacy is mediated by rapid achievement of peak plasma concentrations (C_{max}) after SC administration. Relistor does not accumulate after multiple doses, and there are no known drug-drug interactions (DDIs) that increase its systemic exposure.

Chemical Structure: As shown in Figure 2, Relistor is unrelated in chemical structure to alvimopan. Relistor (like naloxegol, naloxone, and naltrexone) is derived from morphine. In contrast, alvimopan is a derivative of meperidine, a synthetic opioid that has been associated with CV risk (36;37) (see Section 5.1.1).

Figure 2: Structural Differentiation of Relistor and Alvimopan

4,5α-epoxymorphinan class[a]		4-aryl-piperadine class	
Relistor	**Morphine**	**Alvimopan**	**Meperidine**
			

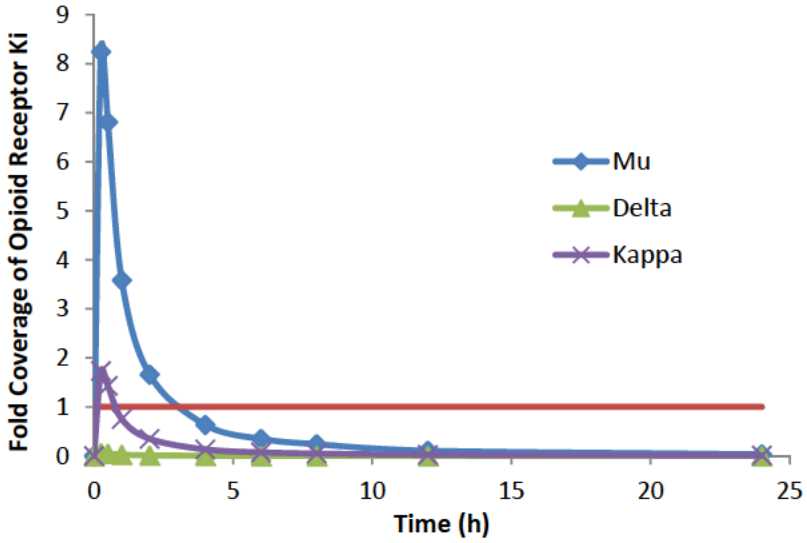
a Other antagonists in 4,5α-epoxymorphinan class include naltrexone (Vivitrol®, Revia®), naloxone (Narcan®), and naloxegol.

In Vitro Pharmacology: Consistent with the differences in structure, these drugs have differential pharmacology, as described in Section 5.0. Specifically, Relistor has shown nearly

undetectable inhibition at the delta opioid receptor, while demonstrating a Ki of 42 nM at the mu opioid receptor. Following 12 mg SC dose administration, Relistor achieves an approximate 8.2-fold coverage of the mu opioid receptor Ki, compared with 0.06- and 1.7-fold coverage of the delta and kappa opioid receptors, respectively (Figure 3), based on unbound plasma concentrations and in vitro receptor Ki.

Nonclinical studies have suggested that delta opioid receptor agonist activity may mediate cardioprotection via ischemic preconditioning. The relatively low affinity (K_i) and free plasma concentration ratio (Figure 3) of Relistor for the delta opioid receptor, combined with Relistor's partial agonist activity, suggest that it would be unlikely for Relistor to antagonize delta opioid receptor mediated cardioprotection *in vivo*. In addition, Relistor has no measurable inhibitory activity at the ORL1 (nociceptin/orphanin) receptor; alvimopan has a reported ORL1 receptor Ki of 470 nM.

Figure 3: Unbound Plasma Concentrations Following a Single SC Dose of Relistor Expressed as Fold Coverage of the Mu, Delta, and Kappa Opioid Receptors



Source: Study MNTX1109

ADME: Consistent with the hydrophilicity mediated by its permanent positive charge, Relistor has a limited volume of distribution (1.1 L/kg), low plasma protein binding, no tissue accumulation, and no evidence of significant penetration or functional activity in the central nervous system. Unlike other peripheral mu opioid receptor antagonists, Relistor is not subject to any known DDIs or food effects that would increase its systemic exposure; it also does not perpetuate any known DDIs. Relistor metabolites appear at low plasma concentrations, do not accumulate in plasma, and do not contribute to its efficacy.

Dosing: In keeping with its PD, Relistor PK after SC administration is characterized by rapid attainment of C_{max} and a short terminal half-life, with no accumulation after multiple doses.

Given that steady-state plasma concentrations are not required for efficacy, the properties of Relistor allow for single dose, PRN administration when relief of constipation is needed.

Safety Assessment: As described in Section 5.0, results from multiple *in vitro* and *ex vivo* studies, along with safety assessment studies in nonclinical species at Relistor doses up to 400 mg/kg and durations of up to 104 weeks, have not indicated an increased CV safety risk. There is no evidence of a signal that predicts an increased human CV risk associated with Relistor in the comprehensive nonclinical and clinical pharmacology data set.

1.5.1 Markers of CV Safety

During the course of its extensive development program, Relistor has been studied in > 150 nonclinical studies and 65 clinical studies (phases 1-4) in over 6000 subjects, including healthy subjects, patients with OIC, and patients with POI. These studies were conducted across a wide range of doses and systemic exposures, including IV doses up to 24 mg IV every 6 hours (Q6H), a daily dose level 8 times higher than that used for OIC, associated with Relistor plasma concentrations exceeding 1000 ng/mL. In the course of assessing potential markers of increased CV risk, Salix has reviewed data across clinical studies as well as *in vitro* studies assessing potential risk factors. In these studies, there was no signal of substantive increases in blood pressure (BP) or pulse (summarized below), increased platelet aggregation, metabolic changes, or corrected QT (QTc) interval prolongation, surrogates typically associated with CV risk (Section 5.4). These findings are consistent with the absence of a clear mechanism for increased CV risk.

The potential for changes in blood pressure and pulse associated with Relistor treatment were evaluated extensively following first dose and during repeat dosing for each of the 3 formulations (SC, oral, and IV) and across all 3 indications (OIC in NCP, OIC in advanced illness, and POI). BP and pulse were evaluated using measures for acute and long-term change from baseline, potentially clinically significant outliers, and repeated measures analyses incorporating changes relative to acute and chronic dosing. Summarized in this briefing document are results from these analyses in 2 populations: the short-term treatment of POI using supratherapeutic IV doses, and acute and chronic treatment at therapeutic doses in OIC. The key findings are from the following studies:

- Three phase 3 studies in patients with POI who were treated with IV Relistor up to 24 mg every 6 hours (Q6H; Studies MNTX 3301, 300, and 301).
- Two phase 3 studies in patients with NCP and OIC treated with SC Relistor 12 mg (sNDA Studies 3356 and 3358).

Overall, the BP and pulse data from clinical studies are consistent with observations in the animal data. More specifically, Relistor has mild vasodilatory properties at supratherapeutic doses and negligible to nonexistent changes in BP and pulse at therapeutic doses used in the treatment of OIC.

1.6 Overview of the Clinical CV Safety Profile of Relistor

Among the opioid receptor antagonists in development for OIC, Relistor has been the most extensively evaluated in the nonclinical, clinical, and post-marketing settings. In assessing the CV safety profile of Relistor, Salix began with analyses of all reported MIs and all-cause mortality which are believed to be the most reliable or "hardest" endpoints. Neither the Relistor nor alvimopan studies prospectively adjudicated CV outcomes.

While the single study with alvimopan did suggest a potential CV safety issue at that time, current data do not support a class effect that would necessarily extrapolate to Relistor or other members of the class:

- The imbalance in serious CV events arising from the single alvimopan trial has not been observed in the development programs of any other peripheral opioid receptor antagonists or in any of the other studies in the alvimopan development programs.

- No potential CV signal has been seen in the Relistor clinical trials dataset, which includes > 6000 subjects or in the Relistor post-marketing experience which includes > 800,000 patient exposures representing more than 15,000 person years of exposure (PY).

- The event rate of MIs in the 48-week, open-label Relistor NCP safety trial (Study 3358) was consistent with expected event rates in the NCP population taking opioids based on the published literature and included nearly twice the amount of patient exposure data compared with alvimopan Study GSK014.

- While Relistor and alvimopan share a therapeutic mechanism of action for OIC, these drugs are unrelated in structure and have differential pharmacology. Relistor is in the subclass of mu opioid antagonists derived from morphine, whereas alvimopan is derived from meperidine, a synthetic opioid that has been associated with CV risk factors (36;37).

In the FDA response to the formal appeal, they noted that while no CV signal was apparent in Relistor Study 3358, the open-label design did not allow for interpretation. Salix believes that the event rates observed in this study are interpretable and consistent both long-term studies of naloxegol as well as established rates described in the literature for chronic pain patients on opioids (14;15;34).

There was no apparent causal relationship between Relistor and observed CV events in the studies. Further, the CV safety profile of Relistor is also distinctly different from that giving rise to the potential CV signal for alvimopan in GSK014, both in terms of event rate (see Table 1) and timing of events (Figure 4).

Table 1: Absolute Event Rate for Unadjudicated MACE – Relistor vs. Alvimopan

	Events	Patient-Years of Exposure	Event Rate per 100 PY (95% CI)
Relistor Studies 3356 and 3358	7	668.1	1.05 (0.42, 2.15)
Alvimopan Study GSK014	9	350.9	2.6 (1.18, 4.83)

Abbreviations: MACE = major adverse cardiovascular event; PY = person years of exposure; and CI = confidence interval.
Note: MACE was defined as defined as myocardial infarction, stroke or CV death.

Following an independent, expert post-hoc adjudication of all potential MACE cases, 3 Relistor patients were adjudicated as having experienced MACE in the Relistor studies (0.45 events per 100 PY) during 668 person-years of patient exposure.

Similar to the observations for all MACE, the rate of unadjudicated MIs for Relistor when analyzed separately was identical to the rate seen in the large claims-based study of ~150,000 adults on chronic opioid therapy reported by Carman et al. (34), and markedly lower than observed with alvimopan in GSK014 (Table 2). These findings were also consistent with observations for a long-term study of naloxegol, Kodiac-08 (35). A recent 12-week study of an oral formulation of Relistor (Study 3201; see Section 3.0) evaluated over 800 patients with NCP with OIC and no cases of MI were reported.

Table 2: Event Rate for Unadjudicated MIs: Carman et al., Relistor, and Alvimopan

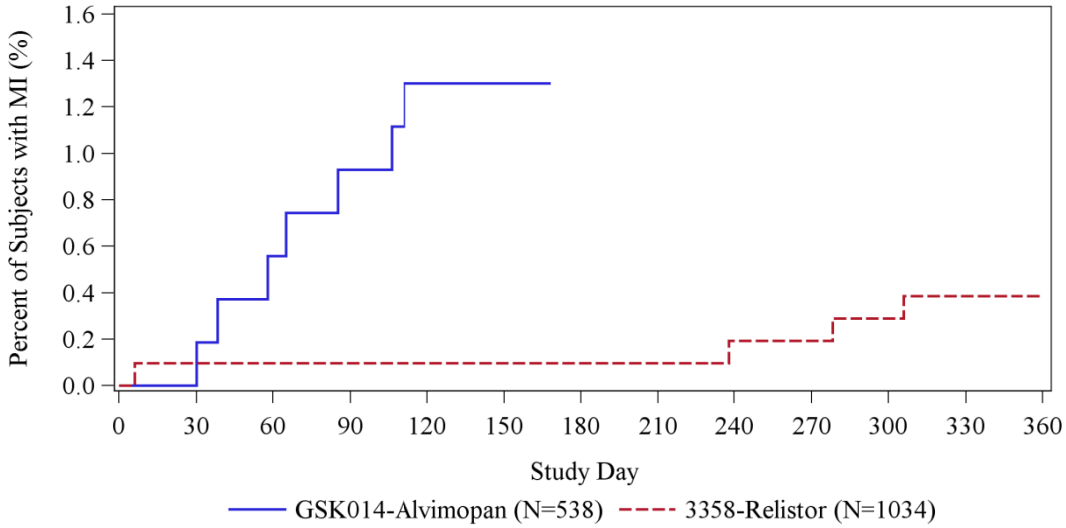
	Number of Events	Patient-Years of Exposure	Event Rate per 100 PY (95% CI)
Chronic Opioid Users with NCP (Carman) (34)	1067	176,732	0.60 (0.57, 0.64)
Relistor Studies 3356 and 3358	4	668.1	0.60 (0.16, 1.53)
Alvimopan Study GSK014	7	350.9	2.0 (0.80, 4.08)

Abbreviations: PY = person years of exposure; and CI = confidence interval.

In addition to differences in event rates in the Relistor and GSK014 studies, there were also differences in time to event for MIs, as shown in Figure 4.

The comparison shown in the figure is between MIs in the active treatment arm for the GSK014 study and the MIs that were reported in the long-term, open-label safety study of Relistor. The profiles of unadjudicated MIs between alvimopan in GSK014 and Relistor during long-term treatment were wholly distinct. The majority of MIs in the GSK 014 study occurred within the first 90 days of treatment and all occurred within 111 days. In contrast, the MIs that were reported in the Relistor long-term safety study occurred at various time points over the course of 48 weeks with no particular pattern identified. These observations should also be put in context with the significantly greater person years of exposure in the Relistor NCP studies versus the GSK014 study (599 PY vs. 351 PY).

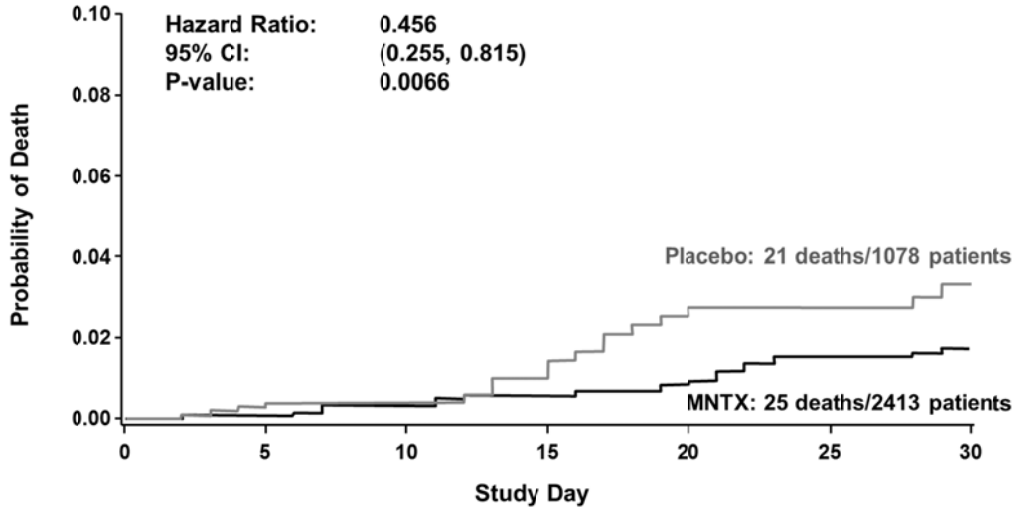
Figure : Time of MI in Relation to Days on Therapy– Relistor Study 3358 vs. Alvimopan Study GSK014



Note: GSK014 data reproduced from 6-month interim analysis reported in FDA medical review of Entereg®.

In an all-cause mortality analysis of all placebo-controlled Relistor studies (~ 3,500 patients) across development programs there was no evidence that Relistor resulted in an increased death rate (see Figure 5). All-cause mortality represents a hard endpoint with no adjudication needed and events not subject to interpretation. The majority of deaths were from progression of underlying disease in advanced illness patients and it is noted that there was only a relatively short follow-up period. However, if Relistor had acute and significant deleterious effects on mortality or CV safety, a markedly different profile of mortality may have been observed.

Figure : All-Cause Mortality in Placebo-Controlled Relistor Studies – Kaplan Meier



Notes: P-value calculated using a Log rank test. The figure includes the double-blind placebo controlled treatment in advanced illness, NCP, and POI with intravenous, subcutaneous, and oral routes of administration.

1.7 FDA Proposed Mechanism for CV Events

DGIEP has suggested that a potential mechanism for the CV events observed in the development programs of the opioid receptor antagonists is opioid withdrawal. They have suggested that potential opioid withdrawal events or suggestive symptoms may be associated with hemodynamic/autonomic nervous system changes that could increase the risk of CV adverse events (AEs) and MACE.

Nonclinical and clinical studies demonstrate that Relistor transport across the blood-brain barrier is restricted and its functional antagonist activity in the central nervous system (CNS) is undetectable (38). Analysis of the incidence of potential withdrawal symptoms (e.g., tremor, hot flush, hyperhidrosis, anxiety, and piloerection), withdrawal symptom scales, and pain scores in the Relistor studies has shown no clear association between Relistor, opioid withdrawal and the occurrence of MACE events. The rate of symptoms which could represent opioid withdrawal as well as the rate of reports of opioid withdrawal were no different in patients taking Relistor when compared to patients taking extended release opioids alone (see Section 7.3). It is recognized that patients taking chronic opioid therapy with physiologic dependence experience episodes of withdrawal.

Most importantly, no clear relationship between potential withdrawal symptoms, hemodynamic effects and CV events has been observed in the Relistor clinical development program or is evident in the published literature on opioid antagonists

1.8 Pre- vs. Post-Approval Strategies to Assess CV Safety Concerns

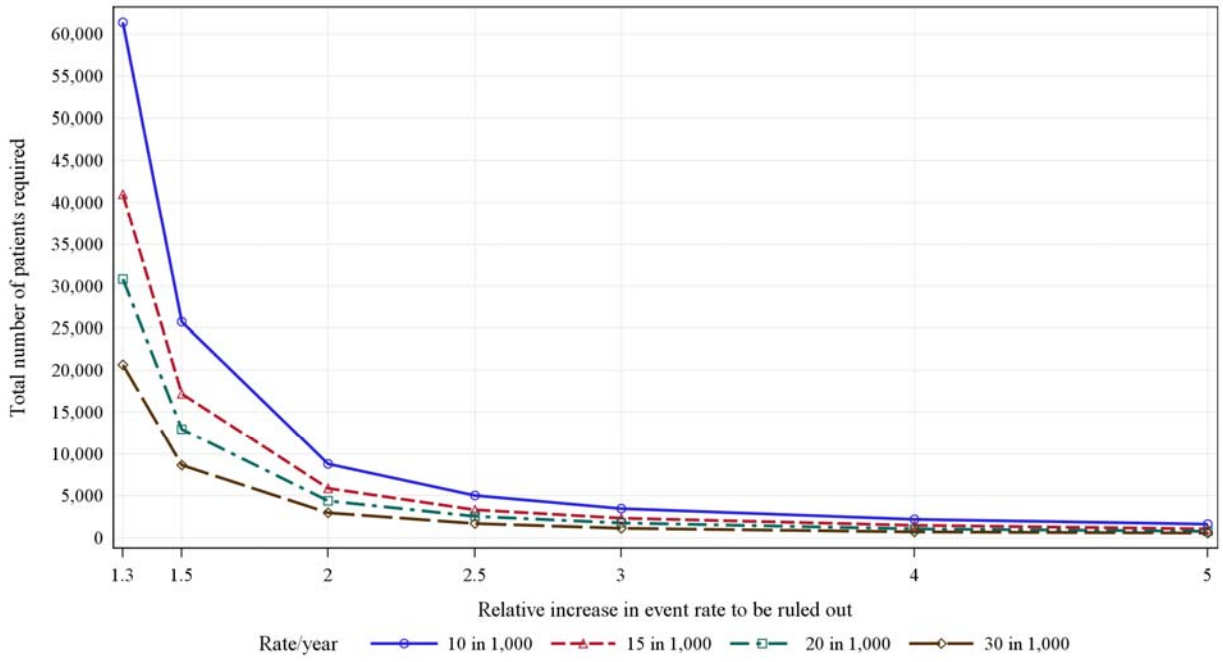
For the Relistor sNDA, DGIEP has required that a CVOT evaluating the relative risk of MACE be completed prior to an approval of the label expansion in the NCP population. Such a requirement would presumably be necessary for all members of this pharmacologic class for this indication. The presumption for this requirement is that a single alvimopan study was a real finding, not due to chance, and that the potential signal is generalizable to all other opioid receptor antagonists despite the fact that other members of this class have never replicated the CV event rate in GSK014.

In totality, the existing Relistor data, publically available long-term data on naloxegol, and the scientific literature on the chronic pain population taking opioids demonstrate a low and consistent event rate for MACE - orders of magnitude below that observed in studies of diabetic patients or those with acute coronary syndrome. As previously noted, there are relative pros and cons to both pre-marketing and post-marketing approaches to further characterize CV risk. Strategies to conduct a pre-market study have been explored. Enrichment of this population in order to potentially achieve higher event rates would require enrollment of subjects with OIC as well as other risk factors such as acute coronary syndrome which would severely impact the ability to enroll the studies as well as impact the ability to generalize the results to the OIC population.

Given the low MACE event rate in the OIC population, there is a considerable risk that such studies, which would require very large sample sizes, may not ultimately provide definitive answers, and unduly delay the availability of an effective therapy in an area of unmet need. There are also issues surrounding variable periods on and off drug with PRN dosing specific to Relistor. Current Relistor labeling reflects QOD dosing as needed when the response to laxatives has been ineffective. In addition, significant study drop-out rates in a symptomatic disease population, which were observed in both the naloxegol Kodiac-08 and GSK014 studies, may also contribute to the reasons why results may be scientifically uninterpretable as well as self-fulfilling for a non-inferiority hypothesis.

When events are rare, the absolute risk difference may be the most suitable measure to use (39). The key determinants for sample size calculation are: a) event rate for the control group; b) increase in the event rate intended to exclude for the comparator; c) power; and d) Type I error. Figure 6 presents an overview of the total numbers of subjects required in a trial to exclude different levels of relative risk based on event rates of 10 in 1,000 per year, 15 in 1,000 per year, 20 in 1,000 per year, and 30 in 1,000 per year. It is worth noting the increases in sample size as the relative risk becomes less than 2.0.

Figure 6: Trial Size versus Relative Risk That Can Be Excluded



Adding to the difficulty in designing a CVOT in this indication, the population of NCP patients on opioids is heterogeneous, comprised of patients with varying comorbid disease states and CV risk factors. While enrollment of high risk CV patients (e.g., recent acute coronary syndrome) could potentially reduce sample size, enrolling patients for such a study would be extremely difficult and not in the clinical interests of the patients. Additionally for Relistor, maintaining the

blind in a long-term CVOT for a symptom-based condition would be difficult due to rapid, predictable achievement of efficacy in the active group and dropouts in the placebo group due to lack of effect.

Given the challenges of conducting a CVOT in this population and the risk that such a study may not provide any further insight, it is the Sponsor's position that concerns related to CV safety in the setting of low event rates could be addressed through labeling and post-marketing studies such as prospectively designed, observational studies utilizing post-marketing surveillance systems.

There is precedent to granting marketing approval for products with a known low and acceptable absolute risk estimate which avoids undue delay for treatments in areas of unmet medical need (39;40). The absolute risk of CV events from the Relistor sNDA studies allows for labeling that provides sufficient information for prescribers and patients. This risk estimate could be further refined in a post-marketing setting (39;41). The absolute risk of CV events during the Relistor development program is consistent with current estimates in this population and also aligned with that observed in a long-term study of naloxegol, a peripheral mu opioid receptor antagonist with pharmacologic similarities to Relistor (15;34;35).

In order to more expeditiously monitor the risk of CV events, a prospective observational study could be utilized across all products in the class with reporting at regular intervals. For example, in similar situations where long-term data has been limited, CV event rates were very low and potential safety concerns have been raised, multi-sponsor registries have been utilized to better assess known risks as well as monitor for any new emerging safety concerns (42). One means of class safety monitoring would be to utilize FDA's Mini-Sentinel project. A representative sample of the population covered by Mini-Sentinel could be monitored with regular intervals chosen for analysis and reporting. The advantage being that with all approved members of the class contributing data, answers regarding any increased risk may be available sooner than those that might be obtained with a large pre-marketing CVOT. More specific to each compound, closed health care networks with common electronic health record systems could also provide for a means to assess an intervention such as introduction of the drug.

While the development program for Relistor has not demonstrated any imbalances or apparent increased risk of CV events, Salix understands the need for outcome data when a class concern is raised regarding the potential for an adverse CV signal. Salix appreciates the opportunity to discuss the necessity, timing, design and size of cardiovascular outcomes trials to support approval of products in the class of opioid receptor antagonists for the proposed indication of OIC in patients with chronic NCP.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations	Definition
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AUC	area under the plasma concentration-time curve
AUC_{0-24}	AUC from time 0 to 24 hours post dose
$AUC_{0-\infty}$	AUC from time 0 to ∞
BID	twice daily
BMI	body mass index
BP	blood pressure
bpm	beats per minute
C_{max}	peak plasma concentration
CI	confidence interval
CNS	central nervous system
CRL	complete response letter
CV	cardiovascular
CVA	cerebrovascular accident
CVOT	cardiovascular outcome trial
DBP	diastolic blood pressure
DDI	drug-drug interaction
DGIEP	Division of Gastroenterology and Inborn Errors Products
ECG	Electrocardiogram
FDA	Food and Drug Administration
GI	Gastrointestinal
HED	human equivalent dose
hERG	human ether-a-go-go related gene
HR	heart rate
IC_{50}	50% inhibitory concentration
IP	Intraperitoneal
IV	Intravenous
K_i	inhibition constant
MACE	major adverse cardiovascular event
METDD	morphine equivalent total daily doses
MI	myocardial infarction
MNTX or MOA	methylnaltrexone (Relistor)

Abbreviations	Definition
M2, M4, M5	methy-6-naltrexone sulfate, alpha-methy-6-naltrexone, and beta-methy-6-naltrexone
NCP	non-cancer pain
NNT	number of patients needed to treat
ODEIII	Office of Drug Evaluation III
OIC	opioid-induced constipation
OOWS	objective opioid withdrawal scale
ORL1	Nociception/orphanin receptor
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
POI	post-operative ileus
PRN	as needed
PY	patient (person) years of exposure
QD	once daily
QOD	once every other day
QoL	quality of life
Q6H	once every 6 hours
QTc	corrected QT
Relistor	methylnaltrexone bromide or MNTX
RFBM	rescue-free bowel movement
SAE	serious adverse event
SBP	systolic blood pressure
SC	Subcutaneous
SD	standard deviation
sNDA	supplemental New Drug Application
SOWS	subjective opioid withdrawal scale
TEAE	treatment-emergent AE
T_{max}	time to C_{max}
$t_{1/2}$	terminal elimination half-life
U.S.	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
V_{ss}	steady-state volume of distribution

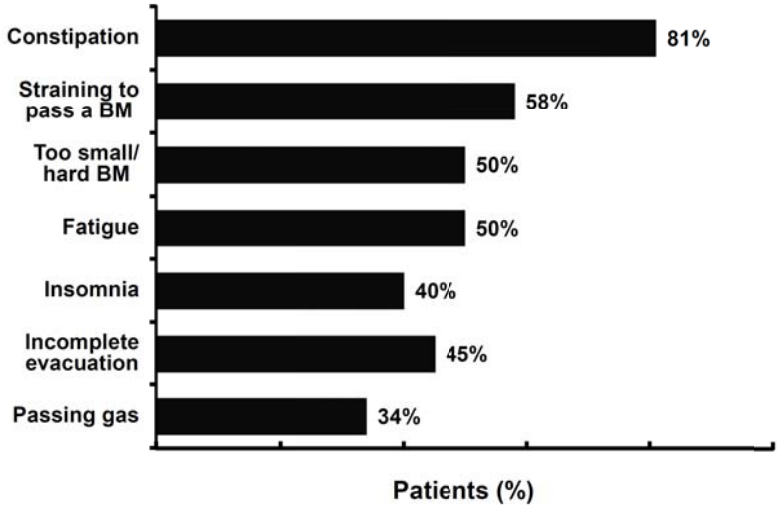
2.0 OIC IN CHRONIC PAIN PATIENTS –UNMET MEDICAL NEED

2.1 Prevalence, Morbidity, and Mortality Associated with OIC

More than 50 million people in the U.S. are partially or fully disabled due to pain (43;44). For patients who suffer from moderate-to-severe chronic pain, opioid analgesics remain an indispensable treatment option (45;46). Opioids are an effective therapy for these patients, with estimates indicating that roughly 3% of adults in the U.S. (~7-8 million people) receive long-term opioid therapy for chronic pain (16). Opioids provide pain relief that enables patients with debilitating chronic pain conditions the ability to maintain some semblance of normal life (46). Chronic pain includes a broad range of conditions, such as traumatic injury, severe musculoskeletal or back pain, neuropathic pain, fibromyalgia, and osteoarthritis pain.

OIC is the most frequent and often most debilitating side effect of chronic pain management with opioids (13;47-51). Estimates indicate that at least 40% of chronic pain patients on opioids experience OIC (3-8), and in contrast with other opioid side effects, tolerance to OIC does not develop with time (9;10). Surveys of opioid users show consistent findings, with a range of 40 to 81% of patients reporting OIC (10;22). In a National Health and Wellness Survey (Patient Reports of Opioid-related Bothersome Effects [PROBE 1 Survey]) (10), constipation was the leading bothersome effect reported by opioid users (81%) and many of the other frequently reported adverse effects were related to constipation symptoms (see Figure 7).

Figure 7: Most-Frequent Opioid Induced Adverse Effects – PROBE 1 Survey



Abbreviations: BM = bowel movement.
Source: Patient Reports of Opioid-related Bothersome Effects [PROBE 1 Survey] (10)

OIC is mechanistically distinct from other etiologies of constipation and is mediated primarily by direct stimulation of myenteric and submucosal mu opioid receptors in the GI tract, leading to a decrease in both GI motility and secretion. Specifically, the binding of opioid agonists to mu opioid receptors interrupts the release of excitatory and inhibitory neurotransmitters, thereby leading to reduced intestinal contractions and reduced mucosal secretions (52-55). The result of

this pharmacologic effect can include infrequent, difficult, or incomplete bowel evacuation often leading to pain and discomfort.

Patients with OIC frequently suffer from debilitating abdominal pain, nausea, tenesmus, bloating, straining, and an ongoing sense of incomplete evacuation (56). Over-the-counter laxatives and other existing therapies do not address the multiple underlying mechanisms of OIC, and are often ineffective, poorly tolerated, and are associated with well-known side effects (e.g., dehydration, vitamin deficiencies, bloating, edema, rebound constipation, laxative dependency, kidney or intestinal damage). When laxatives fail, there are few other treatment options to address OIC and occasionally patients require more invasive measures, such as enemas or manual disimpaction of the rectum (57). Potential serious consequences of refractory chronic constipation include rectal prolapse, bowel obstruction, and GI perforation (58;59).

Findings from the National Health and Wellness Survey indicate that OIC negatively impacts health-related quality of life and productivity. Among patients treated for at least 6 months with chronic opioid therapy, those with OIC scored significantly more poorly than those without OIC on the physical and mental components of the SF-8™ health survey (10). In respondents with OIC, physical and mental components of the SF-8 score were equal to or lower than those observed with other chronic conditions, including migraine, congestive heart failure, diabetes, and depression (10). The burden of illness is also reflected in greater healthcare-related utilization and costs for patients on opioid therapy with constipation compared to patients on opioid therapy without constipation (60;61). In a study reported by Iyer et al., patients with constipation had significantly higher hospital admissions, emergency room visits, home health service use, physician office visits, and laboratory tests relative to demographically matched controls without constipation (Table 3) (60).

Table 3: Healthcare Resource Use in Opioid Patients With and Without Constipation

Parameter	Patient With Constipation (N = 2,519) mean (SD)	Patients Without Constipation (N = 2,519) mean (SD)	p-value
Emergency Room Visits	1.69 (3.38)	0.83 (1.74)	< 0.0001
Physician Office Visits	29.10 (22.83)	20.02 (18.30)	< 0.0001
Days in Nursing Home Care	1.36 (10.68)	0.40 (3.84)	< 0.0001
Days of Home Health Care	13.28 (41.34)	6.57 (26.84)	< 0.0001

Source: Iyer et al. 2010 (60)
Note: Outcomes compared between opioid initiators with constipation and a demographically matched cohort (1:1 ratio) of opioid initiators without evidence of constipation during the 12-month follow-up period.

Constipation has not been definitively established as an independent risk factor for CV events. There appears to be only one study in the literature which cites severe constipation as a potential risk factor for serious CV events. The study identified severe constipation as a risk factor in a secondary analysis of this observational study (> 70,000 post-menopausal women) from the Women's Health Initiative (24). In a clinical setting, patients presenting with

underlying CV disease and constipation with straining are often treated for their constipation in an attempt to reduce the hemodynamic changes associated with straining.

Literature describes the CV effects of straining with constipation related to the Valsalva maneuver (holding one's breath and bearing down) while attempting to pass a bowel movement (25-29). This maneuver leads to a number of acute vascular changes including increased chest pressure, reduced coronary blood flow to the heart, decreases and increases in BP, and changes in heart rate (25-29). Patients taking opioids for chronic pain who develop OIC often present with elevated straining scores. The availability of targeted and effective therapies to reduce the number and severity of straining episodes in this specific population is extremely limited.

2.2 Consequences of OIC on Pain Management and Opioid Dosing

In patients already suffering with chronic pain, uncontrolled OIC symptoms add to their discomfort and may serve as a barrier to effective pain management, prompting opioid dose increases or decreases, opioid discontinuation, or opioid rotation. These changes can all negatively impact a patient's ability to obtain relief from their chronic pain.

Some patients choose to decrease their opioid dose or discontinue opioid therapy altogether rather than experience OIC, leading to inadequate pain control and potentially eliciting a withdrawal response (10;12;13). These patients choose between using their opioids for pain relief while enduring continued constipation, or skipping opioid doses to ameliorate constipation while enduring pain. Other patients with OIC, in response to increasing bowel discomfort and pain, increase their opioid dosage in an attempt to achieve adequate analgesia. This, in turn, can lead to more severe OIC, prompting further dose escalations in an unrelenting cycle. While there is theoretically no ceiling dose for pure opioid analgesics, higher daily opioid doses are associated with an increased risk for overdose, MI, and death (16;17;34).

As the most frequently occurring side effect of opioid use, OIC is also a common reason for opioid rotation. To match a patient with the most effective opioid that provides adequate analgesia with tolerable adverse effects, physicians may rotate patients through different opioid agonists (60;62). There is growing evidence that opioid overdose deaths are the result, in part, of prescriber or patient error during opioid rotation (18-20). Limitations of the equianalgesic dosing tables, inconsistent guidelines, and physician knowledge deficits contribute to the increasing incidence of overdose-related fatalities during opioid rotation.

2.3 Lack of Effective Treatment Options for OIC in Chronic NCP Patients

Over-the-counter laxatives (e.g., bulk agents, stimulants, and osmotic agents) have been the most frequently used traditional therapies for OIC. However, over-the-counter laxatives work via mechanisms that are unrelated to the receptor-mediated effects of opioids (63). Typical regimens combine multiple laxative types, but these are largely unsatisfactory in providing constipation relief to patients who must use high doses of opioids for adequate pain control, and although widely used, have not been shown to be effective in well-controlled trials for OIC. A Cochrane review failed to demonstrate benefit for laxatives in the treatment of OIC (21). In one study of

laxative use in chronic pain patients on opioids, < 50% of those who required laxative therapy achieved a desired laxation response at least 50% of the time (22).

In 2013, Amitiza (lubiprostone), a chloride channel activator, was approved in the U.S. for the treatment of OIC in adults with chronic NCP (23). However, lubiprostone does not fully address the unmet need for OIC treatment in this population and does not target the underlying cause of OIC. The efficacy of lubiprostone was assessed in 3 clinical trials. In the first two trials, for which positive results were obtained, lubiprostone was only marginally effective in treating OIC versus placebo (treatment difference of ~ 8%). In the third study, a treatment benefit versus placebo was not demonstrated. In these studies, the effectiveness of lubiprostone in patients taking diphenylheptane opioids (e.g., methadone) was not established. Further, the studies indicate that lubiprostone's efficacy diminished with increasing opioid doses. The use of lubiprostone in some patients is also limited by nausea, which is the most common adverse effect reported in the Amitiza prescribing information (23).

3.0 RELISTOR CLINICAL STUDIES

3.1 Efficacy of Relistor: NDA, sNDA, and Oral Tablet Studies

In order to ultimately determine if a favorable benefit/risk profile exists for the class of opioid receptor antagonists as a treatment for OIC, the clinical efficacy and degree of benefit needs to be addressed.

The development of Relistor for OIC has included clinical development programs evaluating SC Relistor in the treatment of OIC in advanced illness patients (approved NDA), SC Relistor in the treatment of OIC in NCP (sNDA under appeal), and an oral tablet formulation for OIC in NCP. Table 4 summarizes the study designs and key efficacy results for completed phase 3 studies across these programs. These studies have consistently demonstrated that Relistor treatment provides rapid, reproducible, and reliable relief of OIC in the NCP population and the advanced illness population. In contrast with existing treatment options, SC Relistor provides relief and an effect within minutes or hours for responsive patients. This effect has been shown to be reproducible during repeated long-term use. Predictable laxation is a tremendous benefit to patients who are suffering with immediate and distressing OIC symptoms, or who are homebound due to the unpredictable laxation response associated with other therapies. This reliable response gives patients more control over their daily lives.

Key efficacy findings across these programs include the following:

- Relistor treatment produces a rapid treatment effect. Approximately 30-40% of all active doses in the sNDA studies resulted in a laxation response within 4 hours during double-blind and open-label treatment. Unique to Relistor is the ability to dose on a PRN basis with no apparent attenuation of efficacy over time.
- The observed NNT for benefit for Relistor in OIC studies ranges from 2.5 to 5; by comparison the NNT for Amitiza in OIC ranges from 13 to 50 (23).
- Relistor is effective irrespective of concomitant laxative use. Clinical studies prohibiting concomitant laxative use in the NCP population and allowing concomitant laxatives in the advanced illness population have both demonstrated highly statistically significant treatment effects ($p < 0.001$) versus placebo for primary endpoints.
- Relistor patients have shown consistent and statistically significant improvements during acute and long-term treatment (up to 48 weeks) in weekly RFBMs, constipation symptoms, straining, Bristol stool scale scores, sense of evacuation, and QoL scores.
- Relistor addresses the major limitations of current treatment options with demonstrated efficacy in treating methadone-induced constipation, and in treating OIC in patients taking higher doses of opioids. Relistor's efficacy has been shown to increase with increasing opioid dose.
- Findings for primary efficacy outcomes were consistent in subgroup analyses based on baseline daily opioid dose, underlying pain conditions, and across demographic groups.

Table 4: Phase 3 Studies for Relistor in Patients with OIC

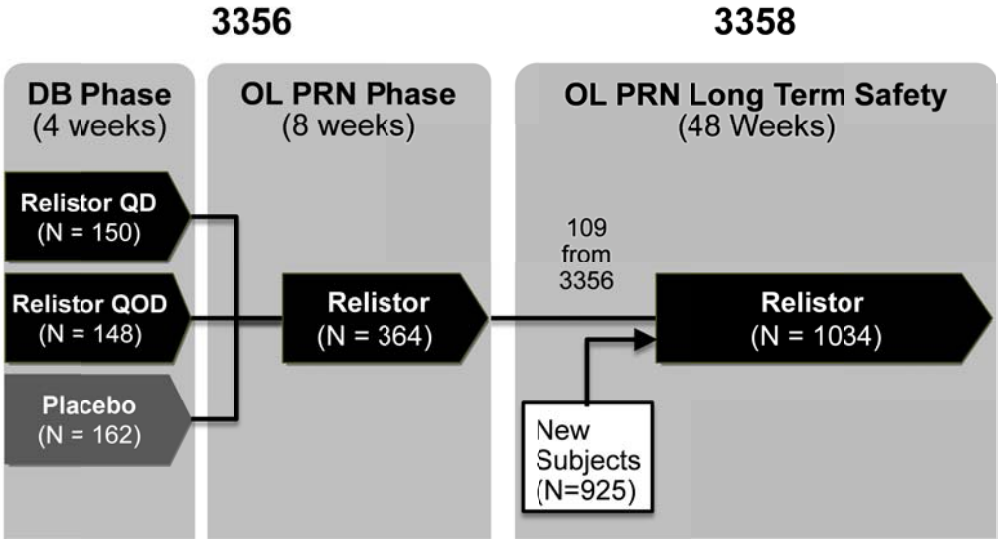
Study ID (# of patients)	Study Design & Duration	Dose Regimens	Key Efficacy Findings
sNDA Studies – SC Relistor in Chronic Non-Cancer Pain Patients			
Study 3356 (N=460)	12-week efficacy and safety study (4-week DB, PC phase and 8-week OL phase)	DB phase: Relistor 12 mg QD or QOD; or Placebo (randomized 1:1:1) OL phase: Relistor 12 mg PRN	• Significantly more Relistor patients achieved a RFBM w/in 4 hrs (34% vs. 10%, p<0.001) of first dose versus placebo. Similarly ~ 30% of all active Relistor doses in each group resulted in a RFBM w/in 4 hrs ($p < 0.001$ vs. placebo). • Significantly more patients in the Relistor 12 mg QD group achieved the endpoint of ≥3 RFBMs per week compared with placebo (59% vs. 38%, $p < 0.001$).
Study 3358 (N=1034)	48-week, OL, safety study	Relistor 12 mg PRN	• Relistor patients had statistically significant improvements from baseline over 48 weeks in weekly RFBMs, straining, stool consistency (Bristol scale), and QoL scores.
Original NDA Studies – SC Relistor in Advanced Illness Patients			
Study 302 (N=134)	14-week efficacy and safety study (2-week DB, PC phase, and 12-week OL phase)	DB phase: Relistor 0.15 or 0.30 mg/kg OL phase: Relistor 0.075 to 0.30 mg/kg PRN	• Relistor-treated patients had a significantly higher rate of laxation w/in 4 hours of first dose than placebo (48% vs. 16%, $p < 0.0001$). • Median time to laxation was 1.0 hr in the Relistor group and 11.2 hrs in the placebo group after first dose.
Study 301 (N=154)	16-week efficacy and safety study (Single-dose DB, PC phase, followed by up to 16 weeks of OL treatment)	DB phase: Relistor 0.15 or 0.30 mg/kg; or Placebo (randomized 1:1:1) OL phases: Relistor 0.075 to 0.30 mg/kg PRN	• Relistor-treated patients in the 0.15 mg/kg group (62%) and the 0.30 mg/kg group (58%) had a significantly higher rate of laxation w/in 4 hrs of first dose than placebo (14%); $p< 0.0001$ for each comparison. • 64% of Relistor patients had improvements in constipation distress versus 33% of placebo.
Oral Relistor in Chronic Non-Cancer Pain Patients			
Study 3201 (N=803)	12-week efficacy and safety study (DB, PC treatment, QD dosing during first 4 weeks, PRN dosing last 8 weeks)	Relistor 150, 300, or 450 mg QD; or Placebo QD (1:1:1:1 randomization)	• Statistically significant improvements were observed for the Relistor 300 and 450 mg/day groups versus placebo in the primary endpoint – average percentage of RFBMs per subject w/in 4 hrs of all doses. • Relistor patients demonstrated statistically significant improvements over 12 weeks in stool consistency, weekly RFBMs, and rectal and stool symptom scales.

Abbreviations: PC = placebo-controlled, DB = double-blind, OL = open-label, SC = subcutaneous, PRN = as needed, QD = once daily, QOD = once every other day, QoL = quality of life, and RFBM = rescue-free bowel movement.

3.1.1 Overview of the Design of sNDA Studies 3356 and 3358

Two phase 3 clinical studies were conducted as part of the development program supporting the label expansion of Relistor to include OIC in patients with NCP. Study 3356, the pivotal study in the clinical program, provided substantial evidence for the efficacy and safety of SC Relistor 12 mg in this indication. Study 3358, a 48-week open-label study, provided confirmation of long-term efficacy and safety. Figure 8 provides a summary of the trial design and number of patients included in each study.

Figure 8: Trial Design and Patients for Relistor Studies 3356 and 3358



Abbreviations: DB = double-blind; OL = open-label; SC = subcutaneous; QD = once daily; QOD = once every other day; and PRN = as needed.

Study 3356

This was the pivotal, double-blind, placebo-controlled study evaluating the Relistor 12 mg SC injection in the treatment of OIC in 460 patients with NCP on stable opioid regimens. Patients were randomly assigned to receive Relistor 12 mg QD, Relistor 12 mg QOD, or placebo in a 1:1:1 allocation ratio. The initial 4-week randomized, double-blind, placebo-controlled period of the study compared the 2 dose regimens of Relistor to placebo. An 8-week open-label phase followed, during which all patients used Relistor 12 mg QD as needed.

A total of 460 patients (Relistor QD = 150, Relistor QOD = 148, placebo = 162) were enrolled and treated in the double-blind period, and 364 patients continued treatment during the open-label period. The majority of patients had a primary diagnosis of back pain; other primary diagnoses included joint/extremity pain, fibromyalgia, neurologic/neuropathic pain, and rheumatoid arthritis. At baseline, patients were on a stable opioid regimen (daily dose ≥ 50 mg of oral morphine equivalents per day) and had OIC (<3 RFBMs weekly and 1 or more of the following; hard or lumpy stools; straining during bowel movements; and/or a sensation of incomplete evacuation after bowel movements). The use of laxatives, enemas, lubiprostone,

prokinetics, bulking agents, and stool softeners was prohibited during the study. Patients were permitted to use rescue laxative therapy if they did not have a bowel movement for at least 3 consecutive days, but rescue laxative use was not permitted within 4 hours of taking study drug.

The mean age of patients in the study was 49 years, approximately 60% of the patients were female and 90% were white. Median baseline daily opioid use was 160 mg oral morphine equivalents.

Study 3358

Study 3358 was a phase 3, open-label study to evaluate the long-term safety and tolerability of the SC Relistor 12 mg injection in the treatment of OIC in NCP patients. The study included a 2-week screening period, a 48-week treatment period, and a 2-week follow-up period. Patients received SC Relistor 12 mg doses in the study. Dosing was required to be at least once per week, but no more frequently than once per day. The mean number of doses per week across patients in the study was approximately 5.

Patients had a history of chronic NCP, were receiving daily opioids for relief of their pain, and were experiencing OIC for at least 1 month prior to screening. Patients also had to satisfy 2 or more of the following criteria during the month prior to screening: hard or lumpy stools for at least 25% of all bowel movements; straining during at least 25% of all bowel movements; a sensation of incomplete evacuation after at least 25% of all bowel movements; use of manual maneuvers (eg, digital evacuation, support of pelvic floor) to facilitate bowel movements at least 25% of the time; and/or fewer than 3 bowel movements per week. The use of laxatives was not prohibited in the study.

A total of 1034 patients enrolled and received at least one dose of Relistor. Of these, 477 patients (46%) completed the 48-week treatment period. There were 557 patients (54%) who discontinued early. The primary reasons for early discontinuation were AE (15%), subject request (13%), subject failure to return (9%), and protocol violation (8%). Demographics and baseline characteristics for the study were similar to those observed in Study 3356. The mean age of patients in the study was 52 years. Approximately 65% of the patients were female, and 90% were white. The most frequent primary pain condition at baseline was back pain (54%).

3.1.2 Summary of Efficacy in sNDA Studies 3356 and 3358

Two co-primary endpoints were defined for the pivotal Study 3356: the proportion of subjects having a RFBM within 4 hours of the first dose, and the proportion of active injections resulting in a RFBM within 4 hours during the double-blind period. A RFBM was defined as a bowel movement that occurred without laxative use during the previous 24 hours.

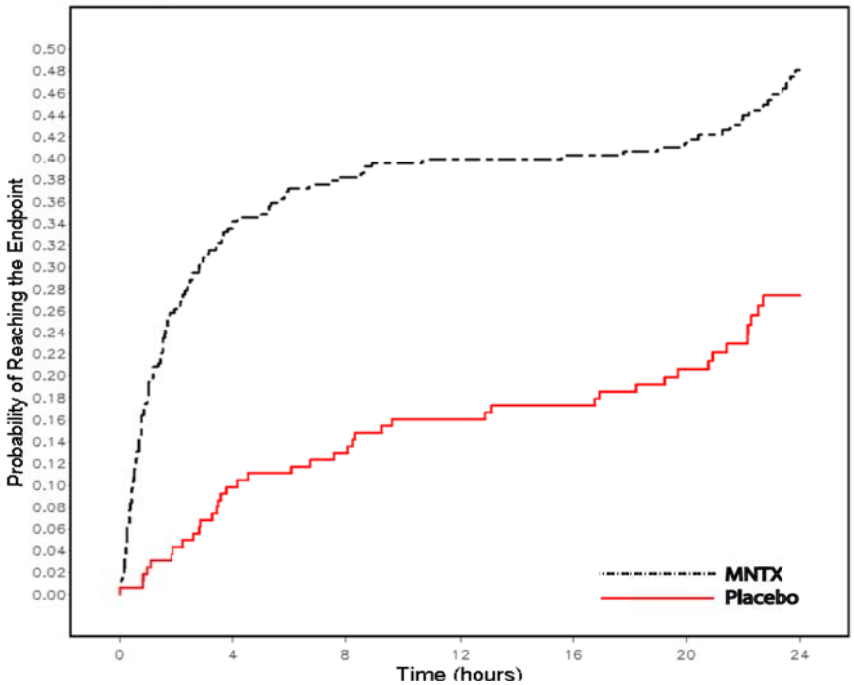
As shown in Figure 1 in the executive summary (Section 1.2), Relistor met each of these co-primary endpoints with clinically and statistically significant differences observed versus placebo. Patients in the Relistor treatment groups had significantly higher rates of RFBMs within 4 hours of their first doses compared to placebo patients (34% vs. 10%; $p < 0.001$). Similarly, the percentages of active injections resulting in RFBMs within 4 hours were

significantly higher in the Relistor QD (29%; p < 0.001) and Relistor QOD (30%; p < 0.001) groups compared with the placebo group (9%). The results for the co-primary efficacy endpoints from this study were robust and comparable to those observed in previously completed studies supporting the approval of Relistor for the treatment of OIC in patients with advanced illness.

In total, 59% of patients in the Relistor 12 mg QD group achieved ≥ 3 RFBM/week compared to 38% in the placebo group (p < 0.001). The proportion of subjects who had ≥ 3 RFBM/week in the Relistor 12 mg QOD group did not attain statistical significance compared to placebo (45% vs. 38%, p = 0.212). The reduced treatment effect for the QOD group was not unexpected for this endpoint given the 'laxation on demand' effect of the drug and limited number of active doses per week in the QOD group. Efficacy analyses looking at response to individual doses of Relistor demonstrated a similar, statistically significant benefit for each active dose in the Relistor QD or QOD groups.

For other key endpoints, the mean change from baseline in weekly SBMs was 3.1 in Relistor 12 mg QD group versus 1.5 in the placebo treatment group during the 4-week double-blind period (p < 0.001). Additionally, time to first RFBM was significantly shorter for patients receiving Relistor 12 mg QD or QOD versus placebo (p < 0.001). Overall, 46% of patients receiving Relistor QD or QOD had a RFBM within 24 hours of first dose of drug versus 25% who received placebo. This difference is illustrated below in a Kaplan-Meier curve (Figure 9).

Figure 9: Time to First RFBM Within 24 Hours of the First Dose of Study Drug – Study 3356



Abbreviations: RFBM = rescue-free bowel movement; and MNTX = methylnaltrexone (Relistor).

Subgroup Efficacy Analyses

Findings for primary efficacy outcomes were consistent in subgroup analyses based on baseline daily opioid dose and on patients' underlying pain conditions, as well as all other demographic characteristics (age, gender, race, ethnicity, and body weight). As shown in Table 5, the Relistor treatment effect versus placebo for patients with laxation within 4 hours of first dose (first co-primary endpoint) was sustained or increased in a subgroup analysis of patients by baseline opioid dose, with greater effect at higher opioid doses. By contrast, Amitiza efficacy findings for this indication showed diminished efficacy with increasing opioid doses (23).

Table 5: Laxation within 4 Hours of First Dose by Baseline Opioid Dose – Study 3356

Baseline Daily Opioid Use (mg)	Treatment	N	N (%)	p-value
< 108	Relistor 12 mg QD/QOD	93	25 (26.9)	0.065
	Placebo	57	8 (14.0)	
108 to < 240	Relistor 12 mg QD/QOD	104	32 (30.8)	0.003
	Placebo	52	5 (9.6)	
≥ 240	Relistor 12 mg QD/QOD	10	45 (44.6)	< 0.001
	Placebo	53	3 (5.7)	

Abbreviations: QD = once daily; and QOD = once every other day.
Notes: Doses of all baseline opioids were converted to oral morphine equivalents. P-values for difference between Relistor and placebo were based on a two-sided Chi-square test.

Long-Term Efficacy

Data from the 48-week, open-label Study 3358 demonstrated durability of response to Relistor. In total, 1034 patients with chronic NCP and OIC participated. Patients were administered Relistor 12 mg QD and allowed to reduce their dosing frequency, if needed, to a minimum of one dose per week. Patients received a mean of ~ 5 doses per week.

Overall, 34% of all injections resulted in bowel movements within 4 hours after dosing. Significant mean increases in bowel movements were also observed versus baseline at each week. These increases (1.5 more bowel movements per week than at baseline) were consistent for every monthly interval during the 48-week treatment period ($p<0.001$ for each monthly interval). Results were consistent across all 12 monthly intervals without evidence of decreased efficacy over time. These findings were supported by laxation assessments, which showed statistically significant improvements from baseline for the Bristol Stool Form Scale, the Straining Scale, and the Sense of Complete Evacuation Scale.

There does not appear to be any reduction in Relistor's treatment effect for OIC over time. Given the reliability and predictability of the response, Relistor is ideally suited for intermittent dosing with patients determining their own need and schedule.

3.2 Safety of Relistor: NDA, sNDA, and Oral Tablet Studies

The safety of Relistor has been established through experience in over 30 clinical studies in OIC and other indications with approximately 6000 patients who received Relistor in oral, IV, or SC doses. In addition, Relistor is currently registered in 57 countries and marketed in 32 countries for the treatment of OIC in patients with advanced illness who are receiving palliative care. It is estimated that > 800,000 patients world-wide have been prescribed Relistor, representing more than 15,000 patient exposure years.

In clinical studies, the patterns of AEs experienced by Relistor-treated patients were generally reflective of expected AEs in the populations under study (e.g., NCP patients, advanced illness patients). Table 6 summarizes the most common treatment-emergent adverse events (TEAEs) which have been observed during randomized, placebo-controlled Relistor studies across clinical development programs for OIC and POI, and during the 48-week, long-term, open-label study for Relistor in the treatment of OIC in NCP patients (Study 3358). For this table, 'common' refers to TEAEs which occurred in ≥ 5% of Relistor- or placebo-treated subjects in the controlled clinical studies, or in ≥ 5% of Relistor subjects in Study 3358. The table also includes AE rates for each group, calculated as events per 100 patient years of exposure. Overall, the events presented in the table were consistent with expectations for the patient populations under study and the Relistor prescribing information. The rates of these most frequent TEAEs were generally lowest in open-label Study 3358, although it should be noted that these comparisons are across populations with varying levels of safety risk. The double-blind pool also includes patients with advanced illness and POI, in addition to NCP patients.

Table 6: TEAEs Occurring in ≥ 5% of Relistor or Placebo Patients in Randomized Controlled Clinical Studies or in ≥ 5% of Relistor Patients in the 48-Week, Open-Label Study 3358

Preferred Term	Placebo (N=1078) (PY=66.9) N (%) [AE Rate]	DB Relistor (N=2413) (PY=182.0) N (%) [AE Rate]	OL Study 3358 (N=1034) (PY=598.7) N (%) [AE Rate]
Nausea	231 (21.4%) [369.0]	510 (21.1%) [299.7]	160 (15.5%) [29.9]
Abdominal pain	52 (4.8%) [80.8]	204 (8.5%) [119.4]	250 (24.2%) [51.7]
Vomiting	100 (9.3%) [153.6]	182 (7.5%) [102.0]	77 (7.4%) [13.3]
Diarrhea	49 (4.5%) [74.3]	121 (5.0%) [68.4]	173 (16.7%) [33.0]
Pyrexia	96 (8.9%) [145.7]	160 (6.6%) [89.1]	22 (2.1%) [3.7]
Headache	47 (4.4%) [71.8]	97 (4.0%) [54.7]	60 (5.8%) [10.5]
Flatulence	34 (3.2%) [52.5]	88 (3.6%) [50.1]	57 (5.5%) [10.0]

Continued

Table 6: TEAEs Occurring in ≥ 5% of Relistor or Placebo Patients in Randomized Controlled Clinical Studies or in ≥ 5% of Relistor Patients in the 48-Week, Open-Label Study 3358 (Cont'd)

Preferred Term	Placebo (N=1078) (PY=66.9) N (%) [AE Rate]	DB Relistor (N=2413) (PY=182.0) N (%) [AE Rate]	OL Study 3358 (N=1034) (PY=598.7) N (%) [AE Rate]
Dizziness	38 (3.5%) [57.3]	80 (3.3%) [44.4]	52 (5.0%) [9.0]
Hyperhidrosis	8 (0.7%) [12.1]	50 (2.1%) [28.0]	93 (9.0%) [16.7]
Back pain	21 (1.9%) [31.9]	55 (2.3%) [30.7]	68 (6.6%) [12.1]
Abdominal pain upper	16 (1.5%) [24.5]	43 (1.8%) [24.0]	70 (6.8%) [12.3]
Upper respiratory tract infection	16 (1.5%) [24.5]	31 (1.3%) [17.3]	62 (6.0%) [10.8]
Influenza	8 (0.7%) [12.0]	19 (0.8%) [10.5]	64 (6.2%) [11.2]
Sinusitis	5 (0.5%) [7.5]	20 (0.8%) [11.1]	56 (5.4%) [9.7]

Abbreviations: DB = double-blind, OL = open-label, AE = adverse event; TEAE = treatment-emergent adverse event, and PY = patient exposure years.
Note: TEAEs are sorted by descending order of frequency across all treatment groups. The AE Rate is calculated as events per 100 patient years of exposure.

3.2.1 SC Relistor in NCP Patients with OIC (sNDA Studies 3356/3358)

Studies 3356 and 3358 include safety data collected in 1364 patients exposed to Relistor for 668.1 PY. A total of 460 patients participated in double-blind, placebo-controlled treatment in Study 3356 (Relistor: 298, placebo: 162), and 364 patients continued treatment during the open-label period. In Study 3358, 1,034 patients received Relistor 12 mg SC for up to 48 weeks, including 109 patients who also participated in Study 3356.

An overview of the safety profile for SC Relistor in the treatment of NCP patients with OIC is provided below. The overall safety profile in this population was consistent with the current Relistor prescribing information. Review of cardiac safety and safety related to the potential for opioid withdrawal are discussed in detail for these studies in Sections 6.0 and 7.0, respectively.

Adverse Events

TEAEs experienced in the clinical development program in NCP patients were consistent with the safety profile of Relistor in the approved label. Many of the most frequent AEs were also consistent with a population of chronic pain patients on opioids, and with induced laxation following Relistor treatment. The majority of AEs in the studies were mild or moderate in intensity. During double-blind treatment in Study 3356, AEs were experienced by 47% of patients treated with Relistor 12 mg QD or QOD, and 38% of patients treated with placebo. Table 7 presents a summary of AEs experienced by ≥ 5% of patients in any treatment group, in the double-blind period of Study 3356.

Table 7: TEAEs with an Incidence ≥ 5% in Any Treatment Group: Double-Blind Treatment in Study 3356

Preferred Term	Relistor 12 mg QD (N=150) n (%)	Relistor 12 mg QOD (N=148) n (%)	Placebo (N=162) n (%)
Abdominal pain	29 (19)	23 (16)	6 (4)
Nausea	13 (9)	17 (12)	10 (6)
Diarrhea	9 (6)	17 (12)	6 (4)
Hyperhidrosis	9 (6)	9 (6)	2 (1)
Vomiting	1 (1)	11 (7)	8 (5)
Abdominal pain upper	2 (1)	8 (5)	4 (3)

Abbreviations: QD=once daily; and QOD=once every other day

During long-term open-label treatment in Studies 3356 and 3358, AEs experienced by ≥5% of patients during the open-label period included abdominal pain (24%), diarrhea (15%), nausea (15%), hyperhidrosis (9%), vomiting (7%), upper abdominal pain (6%), back pain (6%), headache (6%), influenza (5%), and flatulence (5%). The incidence rates for these AEs during long-term Relistor treatment were generally lower or comparable to rates observed during double-blind treatment with Relistor and placebo when normalized for duration.

Serious Adverse Events (SAEs), Deaths, and AEs Leading to Discontinuation

There were no deaths in Relistor or placebo patients in Study 3356. Four (4) deaths occurred in Study 3358 and none were considered related to study drug by the investigator. Of these 4 reported deaths, 3 were reported as CV events that occurred at least 6 days following last recorded dose of Relistor. The other death was reported as a cerebrovascular accident (CVA). These 4 deaths and a summary of all-cause mortality across Relistor clinical development programs are summarized in greater detail in Sections 6.2 and 6.4, respectively. Additional detail on all events of unadjudicated MACE is provided in Appendix 10.2.

Eight patients experienced SAEs during double-blind treatment in Study 3356 (Relistor QD: 5; Relistor QOD: 1; and placebo: 2). SAEs in the Relistor groups included extrasytoles, hematemesis, pancreatitis, pneumonia, road traffic accident, white blood cell count increased, dehydration, hypokalemia, renal cancer, and myoclonus. One patient in the Relistor QD group was diagnosed with renal cancer on Day 4 of the study, and in total experienced 3 of these SAEs (renal cancer, white blood cell count increased, and hypokalemia). The SAE of pancreatitis in the Relistor group appeared to be related to alcohol abuse. Overall, none of these events occurred in multiple Relistor-treated patients. SAEs in the placebo group included hematemesis and musculoskeletal chest pain.

SAEs occurred in 8% of Relistor patients during open-label treatment in Studies 3356 and 3358. SAEs which occurred in > 2 patients were: pneumonia (10 patients); back pain, abdominal pain, chronic obstructive pulmonary disease, dehydration, MI, and non-cardiac chest pain (4 patients

each); and asthma, hypoesthesia, diarrhea, gastroenteritis, hypertension, and nausea (3 patients each).

During double-blind treatment in Study 3356, the incidence of TEAEs leading to discontinuation of study treatment was 8% in the Relistor treatment groups and 3% in the placebo group. The majority of AEs leading to discontinuation were GI disorders. GI events leading to discontinuation in > 2 Relistor patients included abdominal pain (n=8), nausea (n=6), vomiting (n=4), abdominal distension (n=3), and diarrhea (n=3). Hyperhidrosis (n=4) was the only other event leading to discontinuation in > 2 Relistor patients during blinded treatment. During open-label treatment in Studies 3356 and 3358, AEs leading to discontinuation occurred in 13% of patients. The most common of these (> 1%) were abdominal pain, nausea, diarrhea, vomiting, and hyperhidrosis.

Clinical Laboratory Results, Vital Signs, and Electrocardiograms (ECGs)

Mean changes from baseline in hematology, chemistry, and urinalysis parameters did not reveal any clinically meaningful trends over time for any laboratory parameters evaluated; trends for the Relistor groups were similar to those for the placebo group. There were also no notable trends related to changes in vital signs during the studies in central tendency and outlier analyses.

The incidence of potentially clinically significant laboratory values was also low and comparable across treatment groups. The most frequently reported potentially clinically significant laboratory values among Relistor patients during double-blind treatment in Study 3356 were elevated cholesterol, elevated glucose, and elevated triglycerides. The incidence of these potentially significant laboratory values, however, was generally comparable or higher in the placebo group. No notable trends were observed in laboratory values during long-term treatment in Study 3358. There were also no trends suggestive of any hepatotoxic or nephrotoxic drug effects in the studies.

The incidence of prolonged QT interval was low (≤ 1%) and similar for Relistor- and placebo-treated patients during double-blind treatment. The incidence of other ECG-related AEs was <1% for Relistor-treated patients during the double-blind period. Likewise, no notable trends were observed for mean changes from baseline in ECG parameters measured during the open-label period. The incidence of potentially clinically significant QTc interval changes was low (≤ 2%); none of the potentially significant values were considered clinically significant by the investigator. These findings were consistent with the results from the 2 QTc studies which showed no evidence of QT/QTc prolongation or any other deleterious effect on cardiac assessments during Relistor use.

3.2.2 SC Relistor in Advanced Illness Patients (NDA Studies 301/302)

The U.S. prescribing information for Relistor® summarizes safety findings from the pivotal trials which supported the approval of the drug in the treatment of OIC in advanced illness patients (phase 3 Studies 301 [N=154] and 302 [N=134]; see Appendix 10.1). For comparison to NCP patients with OIC in Studies 3356 and 3358, the following are the incidences of AEs, common

AEs, and other safety findings during SC Relistor or placebo treatment in patients with advanced illness and OIC.

Overall, AEs were experienced by 80% of Relistor patients and 68% of placebo patients. AEs with an incidence of ≥ 5% that were reported at least twice as frequently in Relistor versus placebo were abdominal pain (29% vs. 10% placebo), flatulence (13% vs. 6%), nausea (12% vs. 5%), dizziness (7% vs. 2%), and diarrhea (6% vs. 2%).

Deaths were reported for 10% of Relistor patients and 15% of placebo patients. SAEs were experienced by 1% of Relistor patients and 9% of placebo patients. No Relistor patients experienced an SAE in the cardiac disorders system organ class; two placebo patients experienced cardiac SAEs. AEs resulting in early discontinuations from the study were reported for 3% of patients in the Relistor group and 4% of patients in the placebo group. None of these AEs resulting in early discontinuation coded to the cardiac disorders system organ class. There were no meaningful changes in opioid withdrawal measurements (total Himmelsbach scale score and subscale scores) with Relistor treatment following the initial dose or during continued therapy in the advanced illness population. Pain scores also showed no meaningful change during Relistor treatment.

3.2.3 Oral Relistor in NCP Patients with OIC (Study 3201)

For comparison to SC Relistor treatment, the following are the incidences of AEs, common AEs, and other safety findings during treatment with oral Relistor tablets or placebo tablets in Study 3201 in 803 patients with OIC associated with NCP (see Table 4).

AEs were experienced by 59% of Relistor-treated patients and 63% of placebo-treated patients during the 12-week study. AEs that occurred at an incidence of ≥ 5% in the all Relistor group were abdominal pain (Relistor: 8%, vs. placebo: 9%), diarrhea (6% vs. 4%), and nausea (7% vs., 9%).

The incidences of SAEs were 3% versus 4% in Relistor- and placebo-treated patients, respectively. One patient (placebo) experienced an SAE in the cardiac disorders system organ class. No patients in the study experienced a MACE. A total of 3% of Relistor patients versus 5% of placebo patients experienced AEs resulting in discontinuation. None of these AEs resulting in early discontinuation in Relistor patients coded to the cardiac disorders system organ class. Similar changes from baseline in pain scores and opioid withdrawal scores (objective opioid withdrawal scale [OOWS] and subjective opioid withdrawal scale [SOWS]) were observed between Relistor and placebo groups in Study 3201.

4.0 RELISTOR REGULATORY HISTORY

Relistor® is currently licensed by Salix from Progenics Pharmaceuticals, Inc. (Progenics) who developed the compound through a partnership with Wyeth Pharmaceuticals. Table 8 summarizes the U.S. regulatory history of Relistor, including the original NDA approval in advanced illness patients and the sNDA for NCP patients under appeal.

Table 8: Regulatory Review History for the Relistor NDA and sNDA

April 2008	• NDA Approval - RELISTOR® SC Injection approved by FDA for OIC in patients with advanced illness.
June 2011	• sNDA submitted for label expansion to OIC in patients with NCP.
April 2012	• At end of sNDA review, following labeling negotiations, FDA raises concerns about the interpretability of CV events in the 48-week, open-label Study 3358. FDA notes that a different mu opioid receptor antagonist was associated with an imbalance in serious CV events in a 1 year placebo-controlled study. • 90-day sNDA review extension for further evaluation of potential for CV risk.
July 2012	• FDA issues a CRL for the sNDA; requests a CVOT prior to sNDA approval.
October 2012 to May 2013	• End of Review meeting held between Salix and FDA on October 5, 2012. • Salix submits formal appeal to ODEIII and hearing is held on May 7, 2013.
June 2013	• As part of the appeal response, FDA states than an Advisory Committee will be held to discuss the potential for opioid antagonists to cause withdrawal symptoms, the potential CV signal seen with alvimopan, and the potential need and timing of (ie, pre-market or post-market) CVOTs for the class.

Abbreviations: SC = subcutaneous; OIC = opioid-induced constipation; FDA = Food and Drug Administration; CRL = complete response letter; CV = cardiovascular; CVOT = cardiovascular outcome trial; sNDA = supplemental New Drug Application; NCP = non-cancer pain; and ODEIII = Office of Drug Evaluation III.

4.1 Relistor Approval for Advanced Illness Patients with OIC

The Relistor SC Injection was initially approved by the FDA as Relistor® in 2008 for the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. In the Summary Basis of Approval, the FDA noted that "Relistor was clearly superior to placebo" for the primary endpoint of rescue-free laxation response. The agency also noted in its review that "the safety profile [of Relistor] did not pose unique concerns beyond those applicable to other opioid receptor antagonists that are approved and marketed in the U.S" (64). Since the approval in the U.S., Relistor has been approved for this indication in over 50 countries worldwide.

4.2 sNDA for Label Expansion to NCP Patients with OIC

A clinical program was completed in 2011 to expand the Relistor indication to include the treatment of OIC in patients with NCP. This clinical program was conducted in concordance

with applicable U.S. regulatory guidance, and with input from the FDA on study design for the pivotal, placebo-controlled Study 3356, and the long-term, open-label Study 3358. These trials demonstrated a statistically significant and clinically meaningful benefit for OIC, with a safety profile consistent with the existing Relistor prescribing information. Accordingly, Progenics submitted the sNDA on June 27, 2011. Progenics later transferred the sNDA to Salix.

Following label negotiations near the end of the sNDA review period, the DGIEP contacted Salix and expressed concerns about the interpretability of CV events observed in open-label Study 3358. The Division noted that another peripheral mu opioid receptor antagonist had shown an imbalance in serious CV events in a 1-year, placebo-controlled trial. Based on publically available data (30), Salix became aware that the drug referenced by FDA was alvimopan (see Section 1.4).

4.3 CRL and Post-Action Meeting

Following a 90-day review extension, the DGIEP issued a CRL on July 27, 2012. The issues identified were the potential CV signal seen with another member of the class and the lack of an adequate control group (placebo) in the Relistor long-term trial to allow for interpretation of CV events observed in the study. The Division requested that a randomized, controlled CVOT evaluating the risk of MI, stroke and CV death in the population be conducted and completed prior to the approval of the sNDA.

An End of Review meeting was held between Salix and the Agency on October 5, 2012 to discuss the CRL. At that meeting, Salix expressed concerns that a pre-marketing CVOT may not necessarily be the best and only option given that the imbalance in the single alvimopan study has never been replicated and may be a chance occurrence. Further, as the existing data for Relistor did not show evidence of a CV signal, Salix expressed concerns about an unnecessary delay in making a safe and effective medication available to meet the well-established medical need in patients with chronic pain suffering from OIC.

4.4 Appeal to the Office of Drug Evaluation III (ODEIII) & Advisory Committee

In April 2013, Salix submitted a formal dispute resolution request to the ODEIII, based on the position that the data submitted in the sNDA was sufficient to support the approval in the NCP population. The potential CV safety signal observed with alvimopan was not evident in any of the Relistor clinical or post-marketing datasets. An appeal hearing was held on May 7, 2013.

In response to the Salix appeal, the FDA concluded that additional input was needed from an Advisory Committee. The FDA indicated that "while there is no CV signal apparent in the Relistor study data," a definitive evaluation could not be made based on the existing uncontrolled long-term data in the submission. The agency concluded that the Advisory Committee was needed to provide input on issues which included the following: the potential for peripheral mu opioid antagonists to cause withdrawal symptoms; the strength of a potential CV signal seen with another peripheral mu opioid antagonist (alvimopan); an evaluation of the CV safety data from the Relistor program; and the need and timing (i.e., pre-approval vs. post-approval) of CVOTs with drugs of this class.

5.0 RELISTOR NON-CLINICAL AND CLINICAL PHARMACOLOGY

Relistor is a peripherally-acting mu opioid receptor antagonist that is structurally similar to opioid antagonists synthesized from paramorphine. Relistor's positively charged structure restricts penetration across the blood-brain barrier (1;2). The adverse effects of opioids on GI function, including constipation, delayed gastric emptying, abdominal discomfort, and nausea are largely mediated by interaction of these drugs with mu opioid receptors on neurons of the enteric nervous system, primarily neurons in the myenteric plexus and submucosal layers of the gut wall (52-54). In the gut, opioid receptor stimulation, primarily of the mu opioid receptors, interrupts transmission within the enteric nerve pathways that modulate muscle contraction needed for peristalsis, secretory function, and stool propulsion (55). The inhibition of motility and secretion in the gut by opioids is a direct action, and is independent of their analgesic actions in the CNS. Data from both nonclinical and clinical studies demonstrate the ability of Relistor to antagonize opioid action in peripheral tissues while sparing their centrally mediated analgesic properties.

The following key findings are described in this section:

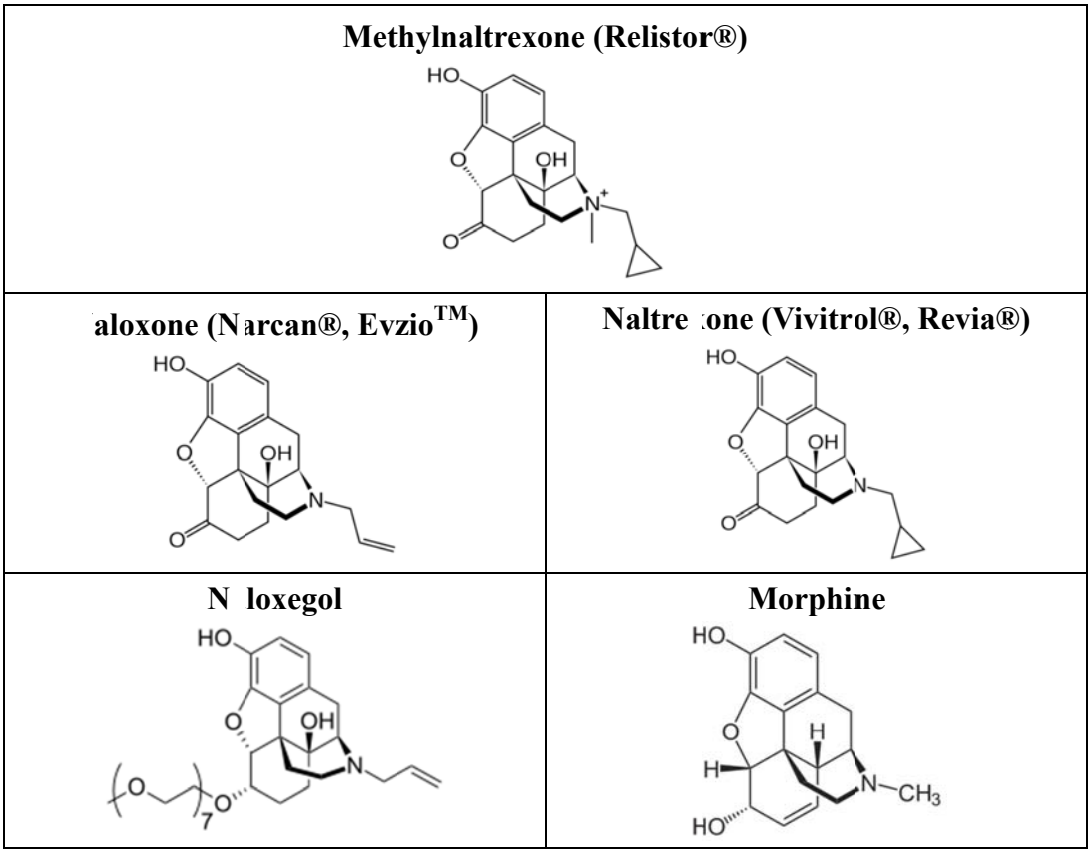
- While Relistor and alvimopan share the same mechanism of action, differences in the structure and pharmacologic activity of the two molecules indicate that CV effects with alvimopan may not be a 'class effect' of opioid antagonists.
- Systemic accumulation of Relistor and its metabolites is not observed after repeat 12 mg SC daily dosing. In contrast, the elimination half-life of the active metabolite of alvimopan is reported to be as long as 18 hours (31), consistent with systemic accumulation after BID dosing.
- Relistor and its primary metabolites specifically inhibit the mu opioid receptor as compared with activity at off target receptors, including the delta opioid receptor and the ORL1 receptor, which have each been associated with a theoretical CV risk.
- The PK properties of Relistor are consistent with its rapid onset and offset of effect. Relistor plasma concentrations reach C_{max} quickly and fall below the mu opioid receptor Ki by approximately 4 hours after SC dose administration; in contrast, plasma concentrations never exceed approximately 7% of the delta opioid receptor Ki, indicating an absence of functional inhibition of the receptor at clinically observed concentrations.
- Non-clinical studies show that Relistor alleviates the peripherally mediated side effects of opioids, particularly the inhibition of GI motility, without affecting centrally mediated analgesia. Non-clinical and clinical data support a lack of CNS penetration.
- Acute and chronic dosing with Relistor does not result in effects on QTc, platelet or metabolic changes, or clinically meaningful changes in BP and pulse, surrogates that are typically associated with CV risk. In addition, comprehensive nonclinical pharmacology and safety assessment programs conducted during Relistor development resulted in no safety signals predictive of a CV safety risk in humans.

5.1 Structure and Receptor Binding Characteristics

Relistor belongs to the 4,5α-epoxymorphinan class of opioid receptor ligands. As shown in Figure 10, Relistor is structurally similar to other opioids antagonists in this class synthesized from morphine (e.g., naltrexone, naloxone, nalorphine). While naltrexone, naloxone and nalorphine work by blocking opioid receptors both peripherally as well as centrally, Relistor has been designed and is useful only as a peripheral opioid antagonist for OIC.

Relistor is formed by the addition of a methyl group to the heterocyclic nitrogen of naltrexone, converting it into N-methylnaltrexone, a quaternary ammonium compound with a permanent positive charge (65). As a result, Relistor has greater polarity and lower lipid solubility than the original naltrexone molecule, both of which restrict its ability to cross the blood-brain barrier. The quaternary ammonium species allows little or no penetration into the CNS, leading to its selectivity as a peripheral opioid antagonist.

Figure 10: Relistor is Structurally Similar to Opioids Synthesized from Paramorphine



5.1.1 Structural Differences between Relistor and Alvimopan

Alvimopan, along with meperidine (also referred to as pethidine in older literature), belongs to the 4-aryl-piperadine class opioid receptor ligands, and has a pharmacophore that can be

differentiated from the 4,5α-epoxymorphinan class to which Relistor belongs. Alvimopan was derived from meperidine (Demerol®), which is the prototypical 4-arylpiperidine opioid agonist. As shown in Section 1.5, alvimopan is structurally dissimilar to the 4,5α-epoxymorphinan class of opioid receptor ligands (including Relistor). Meperidine has been shown to cause decreased cardiac output and cardiac arrest in animal models, and in humans, decreased cardiac output and tachycardia have been noted with meperidine administration. These effects have been associated with a decrease in myocardial contractility (36). With regards to cardiovascular depressant effects, the ratio of lethal dose to effective dose in rats for meperidine is 4.8 compared to 70 for morphine (37).

5.1.2 Relistor Receptor Affinity and Selectivity

Comparisons of Opioid Receptor Binding Affinity

Table 9 presents a summary comparison of opioid receptor binding affinities and selectivity for epoxymorphinan-class molecules, including Relistor, and meperidine derivatives, including alvimopan and its active metabolite. As shown in the table, Relistor is a weak agonist at the mu opioid receptor. Relistor is associated with a mu receptor affinity of 42 nM, a kappa opioid receptor affinity of 200 nM, and a delta opioid receptor affinity of 5690 nM. Relistor has a 135:1 fold selectivity of mu receptor opioid antagonism versus delta opioid receptor antagonism. Alvimopan and its active metabolite ADL 08-0011 show a relatively high affinity for the delta opioid receptor (10 nM and 110 nM, respectively). Given that the active alvimopan metabolite ADL 08-0011 is present at greater systemic concentrations than the parent molecule in humans, and has an elimination half-life (up to 18 hours) consistent with its demonstrated accumulation in the systemic circulation, its binding characteristics are additive to those of the parent molecule (31;66).

Table 9: Opioid Receptor Binding Affinities and Selectivity Index for Epoxymorphinan-class Molecules and Meperidine Derivatives

Compound	Receptor affinities, *Ki* (nM)			Receptor selectivity index (Ratio of μ : δ : κ)
	μ Receptor	δ Receptor	κ Receptor	
4,5α-epoxymorphinan class				
Methylnaltrexone	42	5690	200	1 : 135 : 5
Morphine	1.8	90	317	1 : 50 : 176
Naloxone	1.8	23	4.8	1 : 13 : 3
Naltrexone	1.1	6.6	8.5	1 : 6 : 8
4-aryl-piperadine class				
Alvimopan	0.44	10	100	1 : 23 : 227
Alvimopan metabolite, ADL 08-0011	0.81	110	290	1 : 135 : 358
Meperidine	385	4350	5140	1 : 11 : 13

Source: (67;68); and Study MNIV0101

Comparisons of Agonist Activity

Relistor may also be differentiated from other opioid antagonists based on its intrinsic agonist activity at opioid receptor targets. Table 10 presents a summary of intrinsic opioid agonist activity for Relistor and other opioid antagonists, including alvimopan and naltrexone. Relistor has the highest functional intrinsic agonist activity among opioid antagonists tested, and was the only antagonist tested that showed partial agonist activity at the delta receptor.

Table 10: Intrinsic Opioid Agonist Activity of Opioid Antagonists and Agonists

Compound	Mu	Delta	Kappa
	IA (% of DAMGO)	IA (% of DPDPE)	IA (% of U69593)
Methylnaltrexone	19	3	7
Alvimopan	-7	-15	10
Alvimopan metabolite, ADL 08-0011	-17	-24	6
Naloxone	7	-9	10
Naltrexone	11	-8	18
Morphine	112	88	53

*Intrinsic activity measured as percentage of activity relative to prototypical full agonist at receptor subtype (mu: DAMGO; delta: DPDPE; kappa: U69593) in guanine nucleotide binding assays; (69))

Comparative Binding Kinetics of Opioid Antagonists

Relistor, while having demonstrated affinity, is not as potent as other known opioid antagonists in its interactions with the mu opioid receptor; its binding is rapidly reversible and there is a relatively high rate of association and dissociation at the receptor.

In a published study, the binding of Relistor and other compounds were evaluated by examining the displacement from binding sites of using membranes containing expressed cloned human *mu* receptors obtained from Chinese hamster ovary cells (70). Of the compounds tested, buprenorphine and alvimopan had the slowest dissociation rates (0.016±0.0086 min^{-1} and 0.023±0.0099 min^{-1}) while Relistor had the fastest (1.5±0.44 min^{-1}). Naltrexone had the fastest association rate (100±57 $\mu mol^{-1}min^{-1}$), and Relistor had the slowest (13±4.4 $\mu mol^{-1}min^{-1}$).

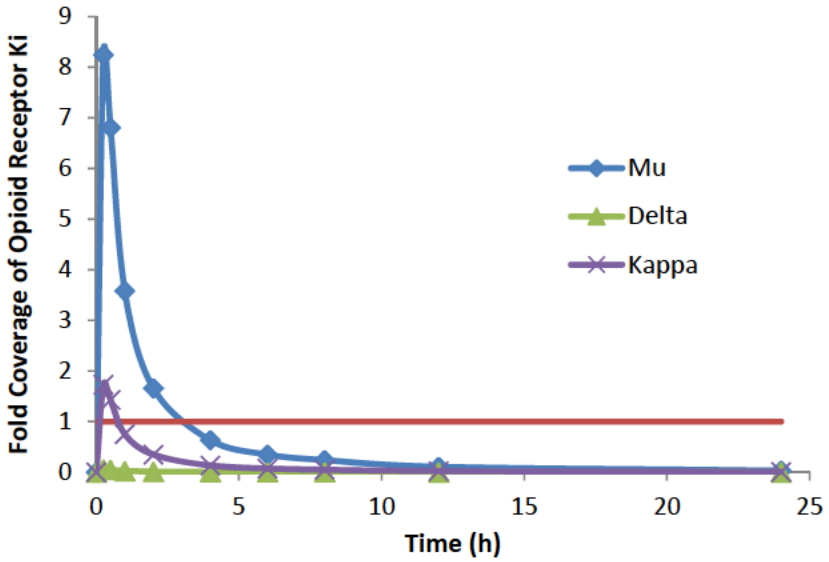
5.1.3 Cardiovascular Effects and Function of Opioid Receptors

In terms of the relationship between opioid receptors and CV effects, nonclinical studies have suggested that agonism of delta opioid receptors may be responsible for cardioprotective effects mediated by an ischemic pre-conditioning mechanism (71). While both delta and kappa opioid receptors are shown to be present in ventricular myocytes of humans and other animals, multiple lines of evidence suggest that the cardioprotective effects of opiates are mediated through activation of delta receptors (71-76). In theory, this cardioprotection could be inhibited by delta opioid receptor antagonism, reversing the infarct-reducing effect of ischemic pre-conditioning

provided by coronary occlusion and reperfusion. It should be noted that the extent to which the cardioprotective effects of delta opioid receptors extends to humans has not been established.

Relistor has minimal affinity at the delta opioid receptor (Ki = 5690 nM), and plasma concentrations do not exceed 1 x the delta opioid receptor Ki after SC administration in humans (Figure 11). In contrast, and in keeping with its rapid onset and short duration of effect, a high multiple of the mu opioid receptor Ki is achieved quickly after SC administration of Relistor, and this exposure drops to below the Ki by 4 hours after dose administration.

Figure 11: Unbound Plasma Concentrations Following a Single SC Dose of Relistor Expressed as Fold Coverage of the Mu, Delta, and Kappa Opioid Receptors



Source: MNTX1109

The affinities of alvimopan and its active metabolite, ADL 08-0011 for the delta receptor (Ki = 10 nM and 110 nM respectively) may suggest a greater possibility of weakening or reversing any cardioprotective pre-conditioning by agonism at delta opioid receptors. However, because the PK of alvimopan at the dose developed for OIC has not been published, a direct comparison of alvimopan to the data presented in Figure 11 cannot be made.

In addition to the 3 classic opioid receptors, a fourth receptor was identified in 1994, termed the ORL1 receptor. Unlike alvimopan (Ki = 470 nM) (68), Relistor has no inhibitory activity at the ORL1 receptor. The ORL1 receptor is believed to have a cardio-regulatory function; agonism at peripheral ORL1 receptors has been shown to mediate effects including cardiac chronotropic and inotropic effects as well as vasodilation and inhibition of GI motility (77).

Relistor has been shown to inhibit endothelial cell migration and proliferation, the two key components of angiogenesis, as well as inhibit increases in vascular permeability produced by

edemagenic agents in vitro, via inhibition of signaling in the VEGF-induced angiogenesis pathway in vitro (78-81). Relistor does not bind to VEGF or the VEGF receptor directly, but interacts with the VEGF induced angiogenesis pathway by inhibiting human endothelial cell migration in vitro. As this is a function of mu opioid receptor antagonism of exogenous and endogenous opioid stimulation of this pathway, it is possible that this effect is shared by other opioid antagonists. For example, naltrexone has demonstrated the ability to inhibit VEGF- and opioid-induced endothelial cell proliferation and migration. Conversely, morphine and other opioid agonists have been shown to stimulate this pathway.

Hypertension is one of the most frequently observed adverse effects of VEGF inhibitor therapy (82). It is dose dependent, has been shown to correlate with the potency of VEGFR-2 inhibition, and occurs rapidly, usually within 3 to 10 days after initiation of therapy (83;84). Relistor does not directly inhibit VEGF, and the pattern and magnitude of hypertension associated with direct VEGF inhibition has not been observed with Relistor. Furthermore, the rapid development of hypertension has not been reported with use of other central or peripheral mu opioid receptor antagonists, indicating that opioid antagonism activity in the VEGF pathway is not associated with the development of hypertension.

In summary, the data collectively indicate that Relistor is differentiated from other peripheral or central opioid antagonists, and its pharmacology is not predictive of CV risk.

5.2 Summary of Non-Clinical Pharmacology

5.2.1 Opioid Antagonism - Specificity to Mu Opioid Receptor Subtype

The specificity of Relistor for the mu opioid receptor has been well demonstrated. In a series of *in vitro* assays evaluating binding activity of Relistor against 81 different receptor targets, Relistor bound selectively to human mu opioid receptors with a K_i of 42 nM (equivalent to 15 ng/mL). Relistor had a much lower binding affinity to human kappa opioid receptors (~5-fold less potency) and negligible binding/interaction with the delta receptor. Relistor does not inhibit orphanin receptors or bind significantly to any non-opioid receptors (85) (Study MNIV0101).

The specificity of Relistor for the mu opioid receptor subtype in GI tissue was confirmed in a gastric-brainstem preparation in neonatal rats. Relistor (1, 10, 100, 1000, or 10,000 nM) competitively reversed the inhibitory effects of morphine and those of the selective mu opioid receptor agonist [D-Ala^2,*N*-MePhe^4,Gly^5-ol] enkephalin (DAMGO) in this preparation. However, Relistor was 20-fold less potent against the kappa opioid receptor-selective agonist U-50,488H, and ineffective against the delta opioid receptor-selective agonist [D-Pen^2,D-Pen^5] enkephalin (DPDPE) (86).

While the primary metabolites of Relistor also demonstrate mu opioid receptor antagonism, they are not likely to contribute significantly to clinical pharmacologic activity given that total maximum plasma concentrations for these metabolites constitute < 6% of the C_{max} of the parent compound (see package insert for Relistor in Appendix 10.1) (87).

5.2.2 CNS Sparing of Relistor – Clinical and Nonclinical Studies

Nonclinical and clinical studies indicate that Relistor blocks the peripherally mediated side effects of opioids, particularly the inhibition of GI motility, but does not affect centrally mediated analgesia or opioid tolerance.

A direct antagonist action of Relistor against opioid activity in the gut was demonstrated in *in vitro* studies of isolated guinea pig ilea and human small intestine tissue preparations in which electrically-induced contractions were inhibited by morphine (88;89).

Multiple studies establish the peripheral distribution and selectivity of Relistor and the exclusion of Relistor from the CNS after peripheral injection (i.e., by SC or intraperitoneal [IP] injections). In a tissue distribution study in rats, concentrations in the brain were the lowest of any tissue or specimen following IV administration of ^{14}C-MNTX (10 mg/kg) (90). Similarly, following IV administration of tritium-labeled Relistor at 5 mg/kg to male rats, the mean brain to plasma ratios of radioactivity indicated limited brain uptake (91). Maximum radioactivity was 71.7 ng-eq./g in brain, and 2450 ng-eq/mL in plasma at about 15 minutes post dose. Correction for brain vascular volume in the study indicates that there was essentially no radioactivity in brain (91). Similar results were observed in the rabbit model. Following epidural administration of Relistor (0.66 mg/kg) in rabbits, minimal Relistor was detected in cerebrospinal fluid, and Relistor was undetectable after 20 minutes (92).

Due to the restricted ability of Relistor to cross the blood-brain barrier, centrally-mediated opioid analgesia is spared following systemic administration of Relistor, as demonstrated in several functional studies conducted in a variety of animal species (93-98).

In these studies, IP or SC administration of Relistor did not interfere with opioid analgesia at doses that treated peripherally mediated opioid side effects. Relistor had no effect on analgesia when administered to rats 10 minutes prior to morphine at doses up to 60 mg/kg (580 mg human equivalent dose [HED]). These doses reversed morphine effects on GI transit but had no effect on nociception as measured by the hot plate test (95). Similar results were observed in mice; Relistor (10 mg/kg SC) had no effect on nociception in morphine-treated animals subjected to the hot plate test (96). In a companion study in Sprague-Dawley rats, Relistor had no effect on morphine antinociception at doses up to 30 mg/kg, IP (96).

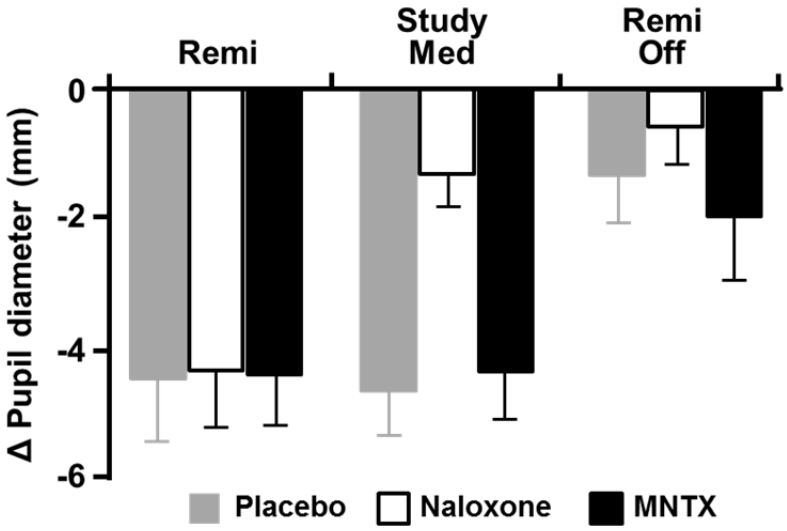
This lack of interference with opioid analgesia is not due to a failure of brain opioid receptors to recognize Relistor. In rats, direct administration of Relistor into the brains of animals was shown to produce opioid antagonism (i.e., reversed analgesia), but did not block analgesia when injected SC (1, 3, or 10 mg/kg) (97). In this study, SC Relistor also produced a dose-dependent antagonism of the delaying effects of morphine on the GI transit time (97).

In humans, a single bolus IV dose of Relistor had no effect on opioid-induced pupillary miosis, confirming that its transport across the blood/brain barrier is restricted (38). In this study, Rosow et al. investigated whether Relistor and another opioid antagonist reversed the central opioid effects of remifentanil in healthy subjects. The investigators relied upon pupillometry to make this determination, as pupil constriction is a sensitive, specific, and commonly used measure of

central opioid effect (99). After receiving 0.15 µg/kg/min of remifentanil, subjects exhibited marked miosis (i.e., pupillary constriction). Subjects then received a single, IV bolus dose of study medication (Relistor, naloxone, or saline).

As shown in Figure 12, naloxone reversed miosis caused by remifentanil (denoted as remi in the figure), but neither placebo nor IV Relistor had this effect. These findings confirm that Relistor did not reverse central opioid effects in the study and that Relistor does not cross into the CNS to a detectable extent in humans.

Figure 12: Relistor Does Not Reverse Opioid-Induced Pupillary Constriction in Humans



Source: Rosow et al. (38)

5.2.3 Lack of Precipitation of Opioid Withdrawal in Animals

Relistor did not produce signs of opioid withdrawal in chronically opioid-exposed mice, rats, dogs, or monkeys. Relistor (1 to 50 mg/kg SC) did not produce behavioral signs of withdrawal (tremor, yawning, restlessness) in acutely opioid-dependent dogs (96), and did not precipitate abstinence syndrome in morphine-dependent monkeys (100). Diarrhea is a common feature of morphine withdrawal syndrome. In rats made morphine-dependent 72 hours prior to testing, Relistor (30 mg/kg SC) did not produce diarrhea (101).

In acutely morphine-dependent mice, Relistor (3, 10, or 30 mg/kg SC) produced weak signs of withdrawal, in contrast to naltrexone, which produced strong withdrawal signs (102). The partial reversal of analgesia at the high dose (~12 times the human equivalent dose) might be due to metabolic conversion of Relistor to naltrexone, which is known to occur at a low but detectable rate in rodents, but which is low in dogs and essentially nonexistent in humans (103).

5.3 Pharmacokinetics and Product Metabolism in Humans

Following SC administration, Relistor is absorbed rapidly, with peak concentrations generally achieved between 15 minutes and 1 hour. Across a range of doses evaluated, peak plasma

concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increase in an approximately dose proportional manner (104). The total bioavailability of a SC Relistor dose (as measured by AUC) appears to be approximately 80% of that observed with Relistor following IV administration, and IV injection is associated with a substantially higher C_{max} (104).

Table 11 presents a summary of single- and multiple-dose PK characteristics of SC Relistor from a study (MNTX1109) in healthy volunteers (105). Over multiple studies, elimination half-life ($t_{1/2}$) estimates have ranged between 6 to 13 hours (104;106;107). This half-life results in a drug washout period of approximately 48 hours.

Table 11: Single and Multiple Dose Pharmacokinetic Parameters [Mean (SD)] for Subcutaneous Relistor 12 mg in Healthy Subjects – Study MNTX1109

Parameters	Relistor 12 mg Single Dose (N=20)	Relistor 12 mg Multiple Dose – 7 Days (N=17)
C_{max} (ng/mL)	140 (35.6)	119 (27.2)
T_{max} (h)	0.29 (0.09)	0.31 (0.11)
AUC_t (ng h/mL)	218 (28.3)	223 (28.2)
AUC_∞ (ng h/mL)	223 (29.1)	NC
AUC_{0-24} (ng h/mL)	218 (28.3)	223 (28.2)
$t_{1/2}$ (h)	5.43 (0.755)	NC
R (%)	NA	105 (6.43)

Study MNTX1109
Abbreviations: AUC=area under the curve; AUC_∞=AUC from time zero to infinity; AUC_{0-24}=AUC from time zero to 24 hours; AUC_t=AUC from time zero to the last quantifiable concentration; C_{max}=peak plasma concentration; SD=standard deviation; $t_{1/2}$=terminal elimination half-life; T_{max}=time to peak plasma concentration. R=accumulation index; SD=standard deviations; NC = not calculated; and NA = not applicable.

Relistor pharmacokinetics in NCP patients in the pivotal Study 3356 were similar to observations in healthy volunteers (Table 12).

Table 12: Single Dose Pharmacokinetic Parameters [Mean (SD)] for Relistor in Patients with Chronic Non-Cancer Pain (Study 3356)

Treatment Group	C_{max} (ng/mL)	T_{max} (h)	AUC_t (ng.h/mL)
Relistor 12 mg QD (N=16)	80.7 (44.4)	1.1 (0.9, 2.0)	146 (111)
Relistor 12 mg QOD (N=24)	88.5 (51.7)	1.0 (0.0, 2.1)	183 (249)

Study 3356
Abbreviations: AUC_t=area under the curve from time zero to the last quantifiable concentration; C_{max}=peak plasma concentration; T_{max}=time to C_{max}. SD=standard deviations; QD=once daily; and QOD = once every other day.

In addition to the currently approved SC formulation, an oral formulation has been developed. The PK of the oral formulation at the 450-mg dose is consistent with a higher AUC and lower

C_{max} than the SC formulation at a dose of 12 mg when the 2 formulations were dosed in a crossover study in healthy subjects (Table 13).

Table 13: Single Dose Pharmacokinetic Parameters [Mean (SD)] for Relistor in Healthy Human Subjects (Study MNPK1117)

Treatment Group	C_{max} (ng/mL)	T_{max} (h)*	AUC_{∞} (ng.h/mL)
450 mg Oral	39.89 (32.11)	2.00 (0.50 – 6.00)	373.32 (207.36)
12 mg SC	174.01 (61.42)	0.25 (0.25 – 0.68)	269.09 (45.14)

Study MNPK1117; *Expressed as median (range)
Abbreviations: AUC_{∞}=area under the curve from time zero extrapolated to time infinity; C_{max}=peak plasma concentration; T_{max}=time to C_{max}.

Metabolism and Distribution

Relistor undergoes both renal and non-renal excretion and exhibits limited biotransformation. Following SC administration, conversion to alpha- and beta-methyl-6-naltrexols (M4 and M5, respectively) and methylnaltrexone sulfate (M2) are the primary pathways of metabolism in humans. N-demethylation of methylnaltrexone to produce naltrexone does not appear to be significant, representing only 0.06% of the administered dose (108). There are no known drug-drug interactions associated with elevations in systemic exposure to Relistor.

All three metabolites are functional antagonists at the mu opioid receptor *in vitro* with the following rank order of potency: M4 ≈ M5 >> M2 (109;110). None of these metabolites exhibited mu opioid agonist activity. It should be noted that, like Relistor, all three metabolites contain quaternary methyl groups at the ring nitrogen. Therefore, like Relistor, all of these metabolites are expected to be restricted from crossing the blood-brain barrier.

Plasma levels of M2, M4 and M5 are low relative to Relistor, with total metabolite C_{max} < 6% of that observed with the parent compound (see Relistor package insert in Appendix 10.1) (87). The mean C_{max} values of all three metabolites are more than 22-fold lower than the C_{max} of Relistor (105). The low potency of M2 and the low circulating levels of M4 and M5 collectively indicate that parent Relistor is the primary agent responsible for observed clinical pharmacological activity. All metabolites have weak off-target potency (Ki > 5600 nM and > 200 nM at the delta and kappa opioid receptors, respectively) (Study MNIV0101).

Relistor undergoes moderate tissue distribution with the notable exception of restricted distribution into the CNS. The steady-state volume of distribution (Vss) is approximately 1.1 L/kg (111). Relistor is minimally bound to human plasma proteins (11.0 % to 15.3 %) (112). These characteristics are consistent with expectations for a charged, hydrophilic molecule that does not partition or bind significantly to tissues or plasma proteins. In a nonclinical radiolabeled mass balance study in rats no extensive partitioning or prolonged residence of Relistor in tissues, including the heart, was observed.

Excretion

Renal excretion of Relistor accounts for slightly more than half the total clearance (54%); fecal excretion accounts for about 17% of total clearance. Significant radioactivity in the feces following IV administration also suggests the involvement of hepatobiliary secretion and/or GI efflux (108).

Impairment of renal function has a marked effect on the PK of Relistor, including reduced drug clearance (107). Severe renal impairment has been shown to produce an eight- to nine-fold reduction in renal clearance along with a 2-fold increase in exposure (AUC). A 50% dose reduction is therefore required in patients with severe renal impairment. This is the only condition associated with the need for a dose reduction, and described in the PI.

Metabolic clearance of Relistor appears to be secondary (< 10%). Hepatic impairment has no clinically significant effect on the PK or clearance of Relistor (106).

5.4 Cardiac Safety Pharmacology

The CV safety of Relistor has been evaluated extensively in non-clinical and clinical safety studies and no CV safety signals have been observed at doses or systemic exposures that are achieved at clinically relevant doses. Relistor effects on hemodynamic function have been evaluated in both *in vitro* and *in vivo* nonclinical studies, and clinical studies in various patient populations using multiple doses and routes of administration. Analyses in these data include evaluations of pulse, BP, as well as potential effects on QT prolongation. To date, available clinical and non-clinical data show no evidence suggestive of clinically relevant effects on hemodynamic or cardiac function with Relistor treatment.

5.4.1 *In Vitro* hERG Studies

The inhibitory potential of Relistor and active control cisapride on human ether-a-go-go related gene (hERG) K+ currents were evaluated in HEK-293 cells. This *in vitro* model is used to predict the potential for test compounds to prolong the QT interval by inhibiting potassium ion flux. Results demonstrated essentially no interaction between Relistor and the cloned hERG channel (IC_{50} > 1000 nM) (113), resulting in calculated safety margins of greater than 1,865-fold and 3729-fold relative to total C_{max} values at human SC Relistor doses of 0.3 mg/kg and 0.15 mg/kg, respectively; safety margins of greater than 30-fold are considered to be predictive of a minimal risk of QT prolongation (114). In comparison, the positive control (cisapride) was at least 19,600-fold more potent than Relistor as an inhibitor of hERG channels. Furthermore, no activity of Relistor was demonstrated in a rabbit Purkinje fiber assay at concentrations up to 100 µM (115).

5.4.2 Non-Clinical CV Safety Studies

In a canine CV safety pharmacology study using conscious dogs receiving IV Relistor at ascending doses (1, 5, and 20 mg/kg), there were no clinically relevant effects observed on CV function (116). There were dose-dependent, transient decreases in systolic blood pressure (SBP)

in 2 of the 4 animals tested, however these changes were within the normal range of variability for beagle dogs and not considered indicative of CV risk because of the short duration of effect. There was no Relistor-related effect on diastolic BP (DBP) or mean arterial BP at any dose level. Relistor did not produce any alteration in the QTc interval value in 3 of 4 dogs at any dosage; however, 1 dog did show a transient increase in QTc interval duration after administration of 20 mg/kg Relistor. This event was not considered indicative of increased clinical risk given that the systemic Relistor exposures observed in this study at a human equivalent dose of approximately 667 mg were more than 250 times the C_{max} observed clinically following SC administration of Relistor at a 0.3 mg/kg dose. Subsequent thorough QT studies in humans (Section 5.4.3) showed no effects of Relistor on QT/QTc prolongation.

In an anesthetized dog study, Relistor at IV doses up to 25 mg/kg produced mild (<20%) to moderate (20–27%) transient, dose-dependent decreases in BP and heart rate (HR). These changes were observed at a human equivalent dose of 833 mg (approximately 70 times the daily dose studied for the NCP population [12 mg]) (117).

In general these observations were not considered to be indicative of an increased CV risk because many were within the normal range of variability for the species, were short in duration, and occurred at dose levels many times higher than recommended doses in humans. These trends have also not been observed in clinical studies.

The effects of Relistor on human platelet aggregation were characterized *in vitro*. The ability of Relistor to either induce platelet aggregation or to inhibit aggregation induced by adenosine diphosphate, arachadonic acid, platelet activating factor, or prostanoid thromboxane A2 was assessed at physiologic and supraphysiologic Relistor concentrations (0.6 µM and 612 µM, respectively). The results were compared to those observed for naloxone and naltrexone, both of which have been reported to inhibit platelet aggregation (118-120). Relistor, naloxone, and naltrexone did not promote platelet aggregation at any concentration tested. Relistor treatment caused a slight degree of antagonism of platelet aggregation at physiologic and supratherapeutic concentrations (up to 6% and up to 37%, respectively), similar to the antagonism observed with naloxone and naltrexone (Eurofins Study 37101-1).

5.4.3 QT Interval Prolongation Studies in Humans

Two controlled phase 1 studies have evaluated the impact of Relistor on cardiac function. There was no evidence of QT/QTc prolongation or any other deleterious effect on cardiac assessments in these trials.

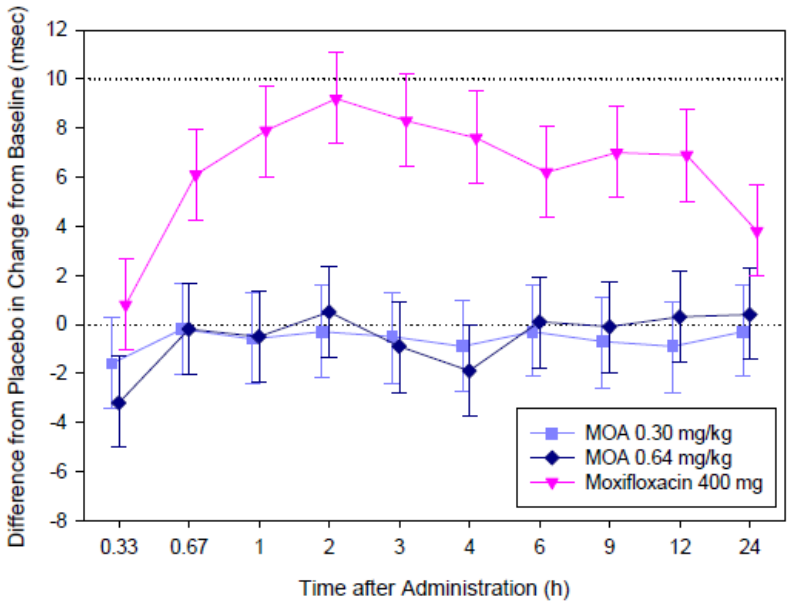
In a large QTc study in 207 healthy human subjects (Study 1106), SC Relistor caused no effect on QT/QTc prolongation at therapeutic doses (0.15 mg/kg and 0.3 mg/kg) or at a supratherapeutic dose (0.5 mg/kg), nor was any effect on secondary ECG variables or wave form morphology observed (121). For both Relistor doses, the 90% confidence for placebo-corrected mean changes from baseline (predose) in QTc intervals excluded 10 msec. In this study, the mean (standard deviation [SD]) C_{max} value was 392 (148) ng/mL, approximately 2.8-fold higher than the C_{max} observed at the therapeutic dose. There was no evidence of QT/QTc prolongation

or any other deleterious effect on any cardiac assessments in Relistor-treated patients. However, this study was inconclusive due to the failure of the positive control to induce the requisite change in QT interval.

Similarly, in a second QTc study (Study 104), Relistor dosed by IV infusion at therapeutic (0.3 mg/kg) and supratherapeutic (0.64 mg/kg) doses resulted in no effect on QT/QTc prolongation (122). In the study, cardiac repolarization was assessed by QTc in 56 healthy adult subjects (mean age = 31 years) who received single IV infusions of 0.3 mg/kg Relistor, 0.64 mg/kg Relistor, and placebo, as well as an oral 400-mg dose of moxifloxacin (positive control). The study included a 28-day inpatient period and each dose was separated by 7 days.

As shown in Figure 13, single IV doses of Relistor at 0.3 and 0.64 mg/kg did not produce any evidence of an effect on QT/QTc prolongation versus placebo. For both Relistor doses, the 90% confidence for placebo-corrected mean changes from baseline (predose) in QTc intervals excluded 10 msec. The largest mean differences from placebo in change at baseline were -0.2 msec (-2.0 msec, 1.7 msec for the 0.3 mg/kg and 0.64 mg/kg doses, respectively) at 40 minutes postdose and 0.5 msec (-1.4 msec, 2.4 msec) at 2 hours postdose, respectively. In this study, the mean (SD) C_{max} value achieved at the supratherapeutic dose was 1062 (258) ng/mL approximately 7.6-fold higher than the C_{max} achieved at the therapeutic dose. Assay sensitivity with the positive control moxifloxacin was demonstrated, validating the study.

Figure 13: QTc Study 104 – Difference From Placebo in QTc Interval Change from Baseline (Mean and 90% CI)



Abbreviations: MOA = methylnaltrexone or MNTX (Relistor); CI = Confidence interval.

5.4.3.1 ECG Assessments in the sNDA Clinical Trials

As discussed in Section 3.2.1 the incidence of AEs of prolonged QT interval was low (≤ 1%) and similar for Relistor- and placebo-treated patients during double-blind treatment in Study 3356. Similarly, the incidence of potentially clinically significant QTc interval was low (≤ 2%) and none of the potentially significant values were considered clinically significant by the investigator. These trends were consistent during long term treatment in Study 3358.

5.4.4 Blood Pressure and Pulse in Clinical Trials

Blood pressure and pulse has been extensively evaluated in Relistor following first dose and during repeat dosing in each of the 3 formulations (SC, oral, and IV) and across all 3 indications (OIC in NCP and advanced illness patients, and POI). BP and pulse has been evaluated using measures for acute and long-term change from baseline, potentially clinically significant outliers, and repeated measures analyses incorporating changes relative to acute and chronic dosing.

Summarized here are results from BP and pulse changes from baseline in 2 populations: the short-term treatment of POI using supratherapeutic IV doses; and acute and chronic treatment at therapeutic doses in OIC. The key findings are from the following studies:

- Three phase 3 studies in patients with POI who were treated with IV Relistor up to 24 mg every 6 hours (Q6H; Studies MNTX 3301, 300, and 301).
- Two phase 3 studies in patients with NCP and OIC treated with SC Relistor 12 mg (sNDA Studies 3356 and 3358).

Overall, the BP and pulse data from clinical studies are consistent with observations in the animal data. More specifically, Relistor has mild vasodilatory properties at supratherapeutic doses and negligible to nonexistent changes in BP and pulse at therapeutic doses used in the treatment of OIC.

High-Dose, Intravenous Relistor in POI Patients

Pulse and BP were evaluated versus placebo at high IV Relistor doses in a large number of patients (N=1,421) who participated in three phase 3 studies evaluating Relistor for the treatment of POI. The Relistor doses evaluated in these studies, up to 24 mg IV Q6H, were markedly higher than the 12 mg QD SC dose established for the treatment of OIC. Based on a phase 1 bioavailability study of SC versus IV Relistor administration, these IV doses were predicted to achieve plasma concentrations that were> 5-fold higher than plasma concentrations observed with SC Relistor 12 mg QD.

Table 14 presents a summary of mean pulse (beats per minute [bpm]) and supine BP (mmHg) changes from baseline on Day 1 and Day 3 in the POI studies. At high Relistor doses there were only small increases in pulse and small decreases in supine SBP and DBP. The small increases in pulse may have been reflexive changes secondary to the small decreases in BP. Mean changes from baseline were generally low, and there were no remarkable differences between the Relistor and placebo groups. There was also no apparent effect of dose on pulse or BP.

Table 14: Mean (SD) Change from Baseline Values for Supine Pulse and Blood Pressure –IV Studies in POI (MNTX3301, MNTX300, MNTX301)

Parameter	IV Relistor 12 mg Q6H (N=474)	IV Relistor 24 mg Q6H (N=476)	Placebo (N=471)
Pulse (bpm) – mean (SD)			
Baseline	77.8 (14.59)	77.5 (15.40)	77.9 (16.03)
Day 1 Change	1.7 (12.56)	3.2 (12.67)	1.6 (12.0)
Day 3 Change	9.4 (19.64)	10.6 (20.64)	10.1 (19.34)
Systolic BP (mmHg) - mean (SD)			
Baseline	137.9 (21.96)	138.7 (22.51)	138.8 (21.12)
Day 1 Change	-3.6 (18.18)	-3.4 (17.51)	-0.7 (16.11)
Day 3 Change	-2.1 (26.29)	-1.4 (27.12)	-0.4 (26.49)
Diastolic BP (mmHg) - mean (SD)			
Baseline	77.4 (13.65)	75.5 (13.98)	75.5 (14.44)
Day 1 Change	-4.7 (12.54)	-3.4 (12.51)	-2.3 (11.0)
Day 3 Change	-4.2 (16.91)	-2.5 (17.56)	-2.8 (18.22)

Source: Studies MNTX3301, MNTX300, MNTX301
Abbreviations: IV = intravenous; POI = post-operative ileus; bpm = beats per minute; SD = standard deviation; BP = blood pressure; and Q6H = every 6 hours.

Table 15 presents a summary of outliers for pulse and BP parameters over 10 days of observation in the POI studies. At the individual patient level there were no apparent differences from placebo in the incidence of potentially-clinically significant decreases or increases in pulse or BP at the high Relistor doses evaluated in these studies.

Table 15: Outliers: Supine Blood Pressure and Pulse – IV Studies in POI (MNTX3301, MNTX300, MNTX301)

Parameter	IV Relistor 12 mg Q6H (N=474) n (%)	IV Relistor 24 mg Q6H (N=476) n (%)	Placebo (N=471) n (%)
Pulse (bpm)			
N	474	476	470
Bradycardia (decrease of ≥ 15 bpm or rate ≤ 50 bpm)	6 (1.3%)	9 (1.9%)	9 (1.9%)
Tachycardia (increase of ≥ 15 bpm or rate ≥ 120 bpm)	54 (11.0%)	33 (6.9%)	49 (10.4%)
Systolic Blood Pressure - Supine (mmHg)			
N	468	471	468
Decrease of ≥ 20 or SBP ≤ 90	42 (9.0%)	40 (8.5%)	35 (7.5%)
Increase of ≥ 20 or SBP ≥ 180	34 (7.3%)	39 (8.3%)	38 (8.1%)

Continued

Table 15: Outliers: Supine Blood Pressure and Pulse – IV Studies in POI (MNTX3301, MNTX300, MNTX301) (Cont'd)

Parameter	IV Relistor 12 mg Q6H (N=474) n (%)	IV Relistor 24 mg Q6H (N=476) n (%)	Placebo (N=471) n (%)
Diastolic Blood Pressure - Supine (mmHg)			
N	468	471	468
Decrease of ≥ 15 or DBP ≤ 50	56 (12.0%)	63 (13.4%)	54 (11.5%)
Increase of ≥ 15 or DBP ≥ 105	22 (4.7%)	22 (4.7%)	25 (5.3%)

Abbreviations: IV = intravenous; POI = post-operative ileus; bpm = beats per minute; and Q6H = every 6 hours.

Subcutaneous Relistor 12 mg in Chronic NCP Patients– Studies 3356 and 3358

Pulse and BP changes following Relistor administration were also analyzed in Studies 3356 and 3358 in order to better understand potential hemodynamic effects of Relistor in patients taking opioids for chronic pain. During the double-blind phase of Study 3356, there were no consistent, clinically meaningful changes in supine pulse or BP. Additionally, a longitudinal analysis of these parameters also showed no effect of Relistor.

A summary of outliers for supine pulse and BP parameters during the double-blind phase of Study 3356 is presented in Table 16. As shown, potentially-clinically significant changes during placebo-controlled treatment were rare and there were no notable differences versus placebo.

Table 16: Outliers: Supine Pulse and Blood Pressure: Double-Blind Phase-Study 3356

Parameter	SC Relistor 12 mg QD (N=150) n (%)	SC Relistor 12 mg QOD (N=148) n (%)	Placebo (N=162) n (%)
Pulse (bpm)			
Decrease of ≥ 15 or rate ≤ 50 bpm	2 (1.3%)	2 (1.4%)	1 (0.6%)
Increase of ≥ 15 or rate ≥ 120 bpm	2 (1.3%)	2 (1.4%)	4 (2.5%)
Supine SBP (mmHg)			
Decrease of ≥ 20 or SBP ≤ 90	0	1 (0.7%)	0
Increase of ≥ 20 or SBP ≥ 180	0	2 (1.4%)	3 (1.9%)
Supine DBP (mmHg)			
Decrease of ≥ 15 or DBP ≤ 50	1 (0.7%)	1 (0.7%)	0
Increase of ≥ 15 or DBP ≥ 105	5 (3.3%)	2 (1.4%)	6 (3.7%)

Abbreviations: SC = subcutaneous; bpm = beats per minute; mmHG = millimeter of mercury; SBP = systolic blood pressure; DBP = diastolic blood pressure; QD = once daily; and QOD = once every other day.

During open-label Study 3358, small variable increases and decreases in SBP and DBP were observed over time. These changes did not appear to be clinically relevant (Table 17). Additionally, a longitudinal analysis for hemodynamic data in Study 3358 revealed no treatment effect for Relistor on pulse or BP.

Table 17: Mean (SE) Change from Baseline for Supine Pulse and BP (Study 3358)

	N	Pulse (bpm)	SBP (mmHg)	DBP (mmHg)
Baseline – Mean (SD)	1033	72.73 (11.01)	123.21 (14.32)	75.36 (9.36)
Change from Baseline – Mean (SE)				
Day 1	1029	-1.22 (0.24)	1.93 (0.30)	1.30 (0.20)
Week 4	896	0.52 (0.32)	1.29 (0.43)	0.75 (0.29)
Week 8	789	1.16 (0.36)	1.16 (0.48)	1.08 (0.32)
Week 12	734	0.97 (0.36)	0.74 (0.51)	0.36 (0.34)
Week 16	690	1.78 (0.38)	1.23 (0.51)	0.51 (0.34)
Week 24	626	1.37 (0.43)	0.65 (0.56)	0.45 (0.36)
Week 32	584	2.33 (0.45)	1.18 (0.58)	0.36 (0.39)
Week 40	520	1.97 (0.46)	0.73 (0.66)	-0.08 (0.43)
Week 48	436	0.67 (0.50)	0.05 (0.68)	-0.45 (0.45)

Abbreviations: bpm = beats per minute; mmHG = millimeter of mercury; SBP = systolic blood pressure; DBP = diastolic blood pressure; ; SD = standard deviation; and SE = standard error.

6.0 CARDIOVASCULAR ADVERSE EVENTS IN RELISTOR STUDIES

A comprehensive review of the Relistor clinical development program has not identified any potential CV safety signal or potential mechanism for CV risk in the treatment of OIC in the NCP population, or in other populations studied. The sponsor's review of CV safety for Relistor and continuing risk assessment included the following key findings:

- No CV signal has been identified in clinical trials of more than 6,000 subjects or in post-marketing safety reporting in over 800,000 patients world-wide.
- CV AEs observed in the primary studies for OIC in NCP patients were consistent with placebo during double-blind treatment and consistent with published event rates for this patient population.
- The incidence of MACE was consistent with the literature-reported incidence for this population, and all-cause mortality was lower than literature rates. The rate of unadjudicated MACE cases was markedly lower than that of alvimopan in GSK014.
- Analysis of hemodynamic and ECG changes during Relistor use revealed no clinically meaningful effects (see Section 5.4). This included no effects on QTc interval prolongation in definitive QTc studies; and negligible effects, if any, on BP and pulse.
- No correlation between potential opioid withdrawal symptoms and MACE or other CV events was identified.

6.1 Treatment-Emergent Cardiac Adverse Events in Relistor Clinical Studies

The AE profile for Relistor in clinical trials and in the post-marketing safety database does not suggest an increased risk of CV AEs during Relistor treatment. Table 18 presents a summary of CV SAEs that occurred in phase 2 and 3 placebo-controlled Relistor trials, and a comparison of these events to CV SAEs that occurred during long-term, open-label treatment in Study 3358. The rates, expressed in events per 100 PY, adjust for the differences in the total durations of exposure and are the numbers in the square brackets. Total PY were 598.7 in open-label Study 3358, 66.9 in the double-blind placebo pool, and 182.0 in the double-blind Relistor pool.

The double-blind studies detailed here include studies for Relistor in the treatment of OIC in the advanced illness population and in NCP patients, and studies for Relistor in the treatment of POI. In total, the double-blind studies include 2413 Relistor-treated patients and 1078 placebo-treated patients. Patients in these trials received Relistor SC (up to 12 mg QD in NCP and advanced illness), at high IV doses (12 to 24 mg Q6H) in the POI studies, or at various oral doses (up to 600 mg QD). The double-blind Relistor and placebo groups had similar baseline characteristics, including demographics and CV risk factors (see Table 24 in Section 6.4).

Cardiac SAEs were infrequent in the Relistor controlled clinical studies and were not observed at a rate higher than placebo during double-blind treatment. The overall rate of CV SAEs was

lower in Study 3358 (1.5 per 100 PY) than in the double-blind study groups (Relistor: 6.0 per 100 PY; Placebo: 16.5 per 100 PY), however it should be noted that these comparisons are across populations with varying levels of cardiac risk. As noted, the double-blind pool also includes patients with advanced illness and POI, in addition to NCP patients.

Table 18: Cardiac SAEs – Relistor Phase 2/3 Placebo-Controlled Studies and Open-Label Study 3358

MedDRA Preferred Term Groups	Placebo (N=1078) (PY=66.9) N (%) [AE Rate]	DB Relistor (N=2413) (PY=182.0) N (%) [AE Rate]	OL Study 3358 (N=1034) (PY=598.7) N (%) [AE Rate]
Cardiac disorders (SOC)	11 (1.0%) [16.5]	11 (0.5%) [6.0]	9 (0.9%) [1.5]
Acute MI/MI	1 (0.1%) [1.5]	1 (<0.1%) [0.5]	4 (0.4%) [0.7]
Cardiac arrest/Cardiorespiratory arrest	1 (0.1%) [1.5]	1 (<0.1%) [0.5]	1 (0.1%) [0.2]
Cardiac failure congestive	2 (0.2%) [3.0]	2 (0.1%) [1.1]	1 (0.1%) [0.2]
Cardiovascular disorder	0	1 (<0.1%) [0.5]	0
Coronary artery disease	0	1 (<0.1%) [0.5]	2 (0.2%) [0.3]
Cyanosis	1 (0.1%) [1.5]	0	0
Ischemic coronary artery disorders	0	1 (<0.1%) [0.5]	3 (0.3%) [0.5]
Rate and rhythm disorders	1 (0.1%) [1.5]	3 (0.1%) [1.6]	0
Supraventricular arrhythmias	5 (0.5%) [7.5]	1 (<0.1%) [0.5]	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, DB = double-blind, OL = open-label, AE = adverse event, PY = patient exposure years, SOC = system, organ, class, and MI = myocardial infarction.
Note: The AE Rate is calculated as events per 100 patient years of exposure.
Note: MedDRA Preferred Term groupings included the following - Cardiac failure congestive (cardiac failure congestive and congestive cardiac failure aggravated); Coronary artery disease (coronary artery disease and coronary artery disease aggravated); ischemic coronary artery disorders (Prinzmetal angina, angina pectoris, and myocardial ischemia); Rate and rhythm disorders (tachyarrhythmia, tachycardia, and extrasystoles); and Supraventricular arrhythmias (supraventricular tachycardia, atrial fibrillation, atrial flutter).

6.2 MACE in Relistor sNDA Studies

Salix conducted a thorough review of all events of potential CV interest in the studies supporting the sNDA. Neither Study 3356 or Study 3358 were designed as CVOTs and no CV signal was apparent in the nonclinical studies, the development program for OIC in advanced illness or in the world-wide post-marketing experience since 2008. The FDA had not raised any safety concerns including a potential class effect during or after the review of the original NDA until late in the sNDA review. Subsequently, no adjudication committee was deemed necessary in the program and the reported CV events were not evaluated prospectively.

In Study 3356, no patient experienced a MACE in the Relistor or placebo groups. In Study 3358, Salix identified a total of 7 patients who experienced an unadjudicated MACE during the 48 week open-label treatment period.

Table 19 provides additional detail on these unadjudicated MACE cases (listed as Subjects A through G). These events appear to occur randomly and without correlation to timing of drug administration. Six of these patients received at least 50 doses of Relistor prior to the event, with 4 having received at least 200 doses. Of the 7 patients, 5 had not received a Relistor dose for at least 2 days prior to their events, which exceeds 5 half-lives of the drug. Four (4) of these 5 patients experienced an unadjudicated MACE 5 or more days following their most recent Relistor dose.

Three patients were reported to have experienced a nonfatal MI, and each of these patients was restarted on study drug after the event without further incident. Two of these patients completed the study. The third patient continued on study drug until Study Day 274, when the patient withdrew from the trial due to relocation (moved to another city). More detail on these patients is provided in Table 32 in Appendix 10.2.

Table 19: Summary of Unadjudicated MACE in Study 3358

Subject: Event	Age	Doses Prior to SAE	Study Day of SAE	Days Off Drug Prior to SAE	Study Drug Restarted	Outcome
Subject A: MI*	57	291	306	2	Yes	Completed study
Subject B: MI*	59	6	6	0	Yes	Withdrew Early - Patient Relocated
Subject C: Presumed MI*	57	248	278	13	N/A	Death
Subject D: MI (SBO)	81	140	238	5	Yes	Completed study
Subject E: CVA	45	210	211	0	N/A	Death
Subject F: Cardiac arrest	68	57	63	6	N/A	Death
Subject G: Sudden death	46	238	257	7	N/A	Death

Abbreviations: SAE = serious adverse event; MI = myocardial infarction; CVA = cerebrovascular accident; SBO = small bowel obstruction; and MACE = major adverse cardiac event.
Note: Events marked with "*" were adjudicated as MACE in a blinded, post-hoc adjudication by an expert cardiologist.

Independent Post-hoc Expert Adjudication of MACE in sNDA Studies

At Salix's request, William B. White, M.D., Professor at the Calhoun Cardiology Center of the University of Connecticut Health Center, performed a blinded, post-hoc, independent adjudication of MACE in the sNDA studies. Dr. White reviewed all cases that were identified based on FDA requests for any terms suggestive of a possible CV event or potential opioid withdrawal symptom and events including terms included in the Standardized MedDRA Queries (SMQs). In all, 95 patients were identified as meeting any of the comprehensive lists of terms as requested by FDA. Dr. White was provided with the case reports for all of these patients

supplemented by all available information on each case that was obtained from extensive follow-up with the study sites.

Dr. White independently identified the same 7 events as the Salix medical review team as potential MACE cases, but adjudicated that only 3 of the 7 events were substantiated in his opinion as actually being a MACE: non-fatal MI in Patients A and B; and a CV death in Patient C (see Table 19). Based on the population characteristics and the fact that the MACE occurred randomly with respect to time on treatment and time since last dose, Dr. White independently concluded that there was no apparent relationship between MACE and treatment with Relistor for the cases reviewed.

A summary listing of all 7 unadjudicated MACE cases is provided in Appendix 10.2. The table includes CV history and risk factors, adjudication assessment, and notes for each patient.

6.3 Rate Comparison of MACE in Patients on Opioids for NCP

The incidence of MACE in the Relistor studies was consistent with the reported rates of CV events in the general population of chronic pain patients on long-term opioids. The incidence of unadjudicated MACE in Studies 3356 and 3358 was 7 events during 668.1 PY or 1.05 events per 100 PY. When Dr. White's adjudication is considered, the rate is 0.45 per 100 PY. The rate of 1.05 events per 100 PY occurred in a population with the following presenting characteristics: 46% obese (BMI>30), 13% diabetic, 37% prior tobacco users, and 41% with a history of hypertension. Additionally, medical history indicated that at baseline over 40% had a history of CV disease, and approximately 5% or more had renal and/or hepatic disease.

6.3.1 MACE: Relistor vs. Alvimopan (GSK014)

Table 20 presents a comparison of absolute event rates for MACE (defined as MI, stroke or CV death) for Relistor-treated patients in Studies 3356 and 3358 and for alvimopan in Study GSK014. As shown, the event rate for unadjudicated MACE observed with Relistor treatment in these studies was markedly lower than that observed for unadjudicated MACE in the alvimopan group in GSK014. Following adjudication, the event rate for MACE for Relistor was 0.45 events per 100 PY, about one-fifth of that observed for alvimopan. The upper bound of the 95% CI for alvimopan (4.83) was > 2-fold higher than that observed for the upper bound of unadjudicated MACE with Relistor (2.15).

Based on the rate of MACE in alvimopan Study GSK014, MACE would have been expected to occur in approximately 17 Relistor patients in Studies 3356 and 3358. The actual occurrence of unadjudicated MACE in these studies was 7 patients, and only 3 of these patients were considered to have experienced a MACE based on the blinded, post-hoc adjudication.

Table 20: Absolute Event Rate for Unadjudicated MACE– Relistor vs. Alvimopan

	Study Type & Duration	Number of Events	Patient-Years of Exposure	Event Rate per 100 PY (95% CI)
Relistor Studies 3356 and 3358	3356: DB (4 weeks)/OL (8 weeks) 3358: OL (48 weeks)	7	668.1	1.05 (0.42, 2.15)
Alvimopan Study GSK014	DB (52 weeks) 2:1 randomization	9	350.9	2.6 (1.18, 4.83)

Abbreviations: DB = double-blind, OL = open-label, PY = person years of exposure; MACE = major adverse cardiovascular event; and CI = confidence interval.

A review of available background characteristics for these studies indicates that these OIC treatment populations were comparable with respect to demographics and baseline population characteristics. Table 21 provides a summary comparison of baseline characteristics for the 52-week Study GSK014 and the combined Relistor data from Study 3356 (12-week) and 3358 (48-week). As shown, the alvimopan treatment group in GSK014 and Relistor patients in Studies 3356 and 3358 were relatively well matched with respect to population characteristics suggesting that differences were not due to baseline demographics or risk factors.

Table 21: Comparison of Baseline and Demographic Characteristics – Alvimopan Study GSK014 and Relistor Studies 3356 and 3358

Parameter	Study GSK014 (Alvimopan Group, 52-Weeks) N = 538	Studies 3356/3358 (Relistor Up to 48-Weeks) N = 1359
Demographics and Baseline Characteristics		
Mean age (years)	54	51
Range (years)	24 – 93	23 – 83
Female	65%	64%
White	91%	90%
Mean BMI (kg/m^2)	30	31
Mean METDD (mg)	184	200
Baseline Risk Factors		
Obesity (≥ 30 BMI)[a]	40%	46%
Hypertension	41%	41%
Myocardial infarction	6%	4%
Stroke	NR	2%
Diabetes	16%	13%
Prior tobacco use	39%	37%

Source: FDA Summary Review of alvimopan; Relistor Studies 3556 and 3358
Abbreviations: BMI = Body Mass Index; NR = not reported; and METDD = morphine equivalent total daily dose.
a) For Relistor, obesity was defined as BMI ≥ 30. It is unknown if the same definition was used in Study GSK014.

6.3.2 MIs: Relistor, Alvimopan (GSK014), and Case Study (Carman)

A study by Carman et al. has shown that chronic opioid users are at an increased level of risk for MIs above that of a matched cohort not taking opioids, even when matched for other risk factors (34). This claims-based study evaluated a cohort of nearly 150,000 adults on chronic opioid therapy (≥ 180 days), against a matched cohort from the general population. Unlike Relistor Studies 3356 and 3358, the Carman study excluded patients with known history of MI or coronary revascularization procedure. Overall, the Carman population on chronic opioid therapy had an approximate 4-fold relative risk increase for cardiac events above the similarly matched cohort of individuals not taking opioids. For opioid users the rate of MI was 2.7 times that of a similarly matched cohort. However, the overall event rate for MI in those taking chronic opioids was low at approximately 0.6 events per 100 PY.

Findings similar to Carman et al. have been observed in the chronic opioid population by other independent groups (14;15). An increased risk for major CV events and all-cause mortality was demonstrated in a large study of Medicare beneficiaries with chronic NCP (15). In contrast to the 1.05 events per 100 PY in the Relistor studies, patients in this study who used various opioids for 180 days had a risk of major CV events of ~12 events per 100 PY, albeit in a population of patients with advanced age.

Table 22 presents a comparison of absolute event rates for MIs in the Relistor studies and alvimopan (Study GSK014). The event rate from the Carman study is also included for comparison. The event rate for unadjudicated MIs observed for Relistor in Studies 3356 and 3358 was markedly lower compared with the alvimopan treatment group in Study GSK014, and identical to the Carman study of ~150,000 chronic opioid users. Carman et al. calculated the incidence of MI for patients in chronic pain taking opioids to be 6.04 events per 1000 PY or 0.6 events per 100 PY (34). The same rate was observed for Relistor. When expert adjudication is considered the event rate for MIs for Relistor in Study 3358 was 0.30 events per 100 PY.

Based on the rate of MIs in alvimopan in Study GSK014, approximately 13 MIs would have been predicted in Relistor patients in Studies 3356 and 3358, well above the 4 unadjudicated MIs that were reported in these studies. Using the Carman rate, 4 MIs were expected in our studies, and this was the exact number on unadjudicated events reported.

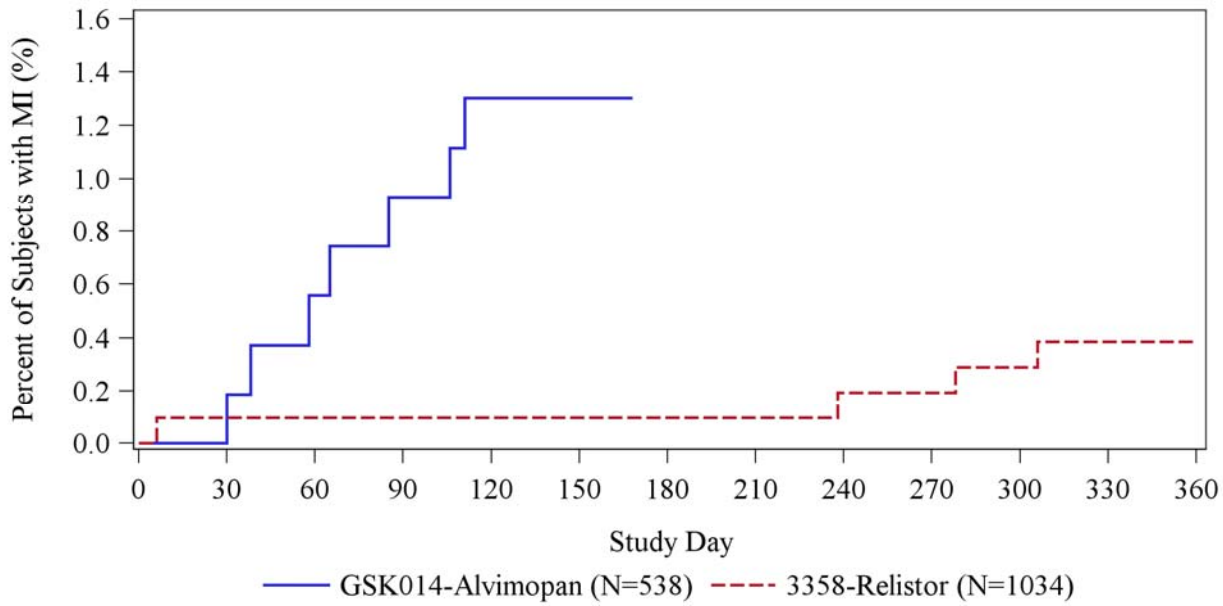
Table 22: Absolute Event Rate for Unadjudicated Myocardial Infarctions

	Study Type & Duration	Number of Events	Patient-Years of Exposure	Event Rate per 100 PY (95% CI)
Chronic Opioid Users with NCP (Carman et al.)	Claims-based study: 3 years	1067	176,732	0.60 (0.57, 0.64)
Relistor Studies 3356 & 3358	3356: DB (4 weeks)/OL (8 weeks) 3358: OL (48 weeks)	4	668.1	0.60 (0.16, 1.53)
Alvimopan Study GSK014	DB (52 weeks) 2:1 randomization	7	350.9	2.0 (0.80, 4.08)

Abbreviations: NCP = non-cancer pain; DB = double-blind, OL = open-label, PY = person years of exposure; and CI = confidence interval.

In addition to differences in event rates in the Relistor studies and alvimopan Study GSK014, there were also marked differences in the profile of time to event for MIs (Figure 14). These observations should be put in context with the greater person years of exposure in the Relistor studies versus GSK014 (668 PY vs. 351 PY).

Figure 14: Time of MIs in Relation to Days on Study Therapy – Relistor Study 3358 vs. Alvimopan Study GSK014



Note: GSK014 data reproduced from 6-month interim analysis reported in FDA medical review of Entereg®.

6.4 Summary of All-Cause Mortality in Relistor Controlled Phase 2/3 Studies

In a review of all controlled Relistor phase 2 and 3 studies across indications and dosage forms, there is no evidence of an increased risk of mortality among patients receiving Relistor versus placebo over a relatively short period of follow-up. In total, these studies include 2413 Relistor - treated patients and 1078 placebo-treated patients who received Relistor in SC, IV, or oral doses in the treatment of OIC or POI. Across studies, 21 of 1078 placebo patients and 25 of 2413 Relistor patients died while on study drug or within 30 days following last dose.

Analysis of all-cause mortality seen in the Relistor clinical database statistically favored Relistor patients over placebo patients, although this difference was driven primarily by deaths observed in studies of Relistor in the treatment of OIC for patients with advanced illness over a relatively short period of follow-up. In a person-time analysis of all-cause mortality (see Table 23), the rate of death per 100 PY was higher among placebo patients (31.4 vs. 13.7) and the ratio of incidence analysis indicated a lower risk for mortality in the Relistor group (0.44; 95% CI: 0.25, 0.78). Figure 5 in Section 1.6 presents a visual impression of these data using a hazard ratio analysis. The hazard ratio for the risk of experiencing death among Relistor patients relative to the risk of death in the placebo group in this analysis was 0.456 (95% CI: 0.255 to 0.815).

Table 23: All-Cause Mortality - Person-Time Analysis in Relistor Randomized Trials

	Placebo N = 1078 (PY = 66.9)	Relistor N = 2413 (PY = 182.0)
Deaths / Rate per 100 PY	21 / 31.4	25 / 13.7
Ratio of Incidence (95% CI)[a]	-	0.44 (0.25, 0.78)
p-value[a]	-	0.0052

Abbreviations: PY = patient years of exposure; and CI = confidence interval.
Note: The table included double-blind placebo controlled phase in advanced illness population, non-cancer pain population, and POI population with intravenous, subcutaneous, and oral routes of administration.
a) Rate on Relistor/ rate on placebo derived from Poisson regression model. P-value derived from Poisson regression model.

Most deaths in Relistor studies have occurred in advanced illness patients, and the majority of these deaths have been related to underlying disease progression. The advanced illness population is notably a potentially vulnerable population. If Relistor had deleterious effects on mortality or CV safety, a markedly different trend in mortality may have been observed.

A review of background characteristics for the randomized studies in this analysis indicates that the Relistor and placebo groups analyzed in the double-blind pool for all-cause mortality were comparable with respect to demographics and baseline population characteristics, including CV risk factors (Table 24). The incidence of serious CV events was also analyzed using these same pooled analysis populations and is presented in Table 18 in Section 6.1.

Table 24: Comparison of Demographic and Risk Factor Characteristics – Pooled Relistor Randomized, Placebo-Controlled Trials

Parameter	Phase 2/3 Placebo (N = 1078)	Phase 2/3 Relistor (N = 2413)
Demographics and Baseline Characteristics		
Mean age (years)	56	55
Female	55%	55%
White	80%	82%
Mean BMI (kg/m^2)	29	29
Mean METDD (mg)	293	373
Baseline Risk Factors		
Obesity (≥ 30 BMI)[a]	37%	39%
Hypertension	52%	48%
Myocardial infarction	14%	14%
Stroke	14%	13%
Diabetes	26%	24%
Prior tobacco use	21%	20%

Source: Double-blind, placebo-controlled IV, SC, and oral route studies with Relistor.
Abbreviations: BMI = body mass index, and METDD = morphine equivalent total daily dose.

7.0 ANALYSIS OF POTENTIAL WITHDRAWAL SYMPTOMS

The DGIEP noted concerns about the potential for drugs in the pharmacologic class of opioid receptor antagonists to cause opioid withdrawal symptoms and suggested a potential link between these symptoms and the occurrence of CV events. However, no relationship has been observed between potential withdrawal symptoms, hemodynamic changes, and CV events in the Relistor data or appears to be evident in the published literature on opioid antagonists.

7.1 Incidence of Potential Withdrawal AEs

In the Relistor studies in chronic NCP patients, the majority of AEs potentially related to opioid withdrawal occurred at a similar rate among Relistor -treated patients and placebo-treated patients.

Potential Withdrawal AEs During Double-Blind Treatment – Study 3356

Table 25 presents a summary of potential withdrawal symptom AEs that occurred in ≥ 2% of the double-blind safety population in Study 3356. Potential withdrawal AEs included in this analysis are those that corresponded to symptoms analyzed in the validated withdrawal scales utilized in the studies (i.e., the OOWS and SOWS). It is noted that the symptoms described in many instances may not be specific to opioid withdrawal and are frequently attributable to concurrent conditions and/or induced laxation, particularly abdominal pain and diarrhea. These symptoms are frequently observed in patients receiving chronic opioid therapy (see Section 7.3).

The majority of potential withdrawal symptoms, as assessed in the OOWS and SOWS, occurred in < 2% of patients overall during double-blind treatment, with no notable treatment differences observed between the Relistor and placebo groups. These less common events included abdominal discomfort, lower abdominal pain, piloerection, cold sweat, insomnia, restlessness, rhinorrhea, flushing, chills, feeling of body temperature change, poor quality sleep, yawning, increased lacrimation, and myalgia.

The incidence of abdominal pain, diarrhea, and hyperhidrosis was higher in the Relistor treatment groups compared with placebo. These symptoms may be in part attributable to laxation in patients with constipation. These events are also reported in the package inserts for Relistor (Appendix 10.1), and for Amitiza (lubiprostone) (23). Notably these events also occur more frequently in Amitiza versus placebo in the chronic idiopathic constipation indication, which is a population not on opioids or at risk for opioid withdrawal. The incidence of other potential withdrawal symptoms (e.g., hot flush, anxiety, tremor) was generally comparable between the Relistor and placebo groups.

Table 25: Potential Opioid Withdrawal Symptom Adverse Events in ≥ 2% of Patients During the Placebo-Controlled Phase of Study 3356

Preferred Term	Relistor 12 mg QD (N=150) n (%)	Relistor 12 mg QOD (N=148) n (%)	Placebo (N=162) n (%)
Abdominal pain	29 (19)	23 (16)	6 (4)
Nausea	13 (9)	17 (12)	10 (6)
Diarrhea	9 (6)	17 (12)	6 (4)
Vomiting	1 (1)	11 (7)	8 (5)
Hyperhidrosis	9 (6)	9 (6)	2 (1)
Upper abdominal pain	2 (1)	8 (5)	4 (3)
Hot flush	4 (3)	5 (3)	3 (2)
Anxiety	3 (2)	3 (2)	3 (2)
Tremor	2 (1)	5 (3)	1 (1)

Abbreviations: QD = once daily; QOD = once every other day.
Note: Table includes double-blind controlled data from Study 3356. Potential Withdrawal AEs include AEs evaluated in the validated OOWS and SOWS questionnaires.

Potential Opioid Withdrawal AEs Over Long-term Subcutaneous Relistor Treatment

During long-term, open-label treatment in Studies 3356 and 3358, the number of patients who experienced potential opioid withdrawal events increased along with the increased duration of observation. However, the rate of these AEs (adjusted for duration of exposure/observation) generally decreased rather than increased with time. Most potential withdrawal AEs (e.g., anxiety, hot flush tremor) were not more frequent with Relistor than with placebo when normalized for duration of observation, and did not occur repeatedly upon repeat dosing as would be expected in opioid-dependent patients if they were related to withdrawal. These withdrawal symptoms also did not necessarily occur together in individual patients and may have occurred at completely different times in the studies.

Table 26 presents results from a data analysis of 5 selected withdrawal symptoms in the phase 3 Relistor studies. These 5 potential withdrawal AEs were selected for analysis by the FDA as part of information requests prior to the CRL for the sNDA. As shown, Relistor -treated patients did not experience these symptoms at a greater rate than placebo-treated patients.

Table 26: Incidence and Rate of Potential Withdrawal Symptoms in Relistor Studies 3356 and 3358

Potential Opioid Withdrawal Symptoms	Placebo Patients (N=162) (PY = 12.1)		Relistor Patients (N=1359) (PY = 668.1)	
	Patients	Rate per 100 PY (95% CI)	Patients	Rate per 100 PY (95% CI)
Any Potential Symptom	8	68.6 (29.9, 131.9)	193	32.5 (28.4, 37.0)
Anxiety	3	25.2 (5.2, 72.3)	41	6.3 (4.5, 8.4)
Hot flush	3	25.3 (5.2, 72.5)	63	9.8 (7.6, 12.5)
Hyperhidrosis	2	16.7 (2.0, 59.2)	116	18.6 (15.5, 22.1)
Piloerection	0	0 (0.0, 30.2)	10	1.5 (0.7, 2.8)
Tremor	1	8.3 (0.2, 45.6)	27	4.1 (2.7, 5.9)

Abbreviations: PY = patient years of exposure; CI = confidence interval.

7.2 Reports of 'Opioid Withdrawal' in Individual Patients

A total of 4 Relistor-treated patients experienced an AE in Studies 3356 and 3358 with a preferred term related to 'withdrawal'. These events were all recorded in Study 3358. Review of SOWS and OOWS scores and overall symptoms before and after the first dose did not support a causal association between first administration and the subsequent report of withdrawal in these patients (see Table 27).

Two Relistor -treated patients experienced an AE of 'drug withdrawal syndrome' in Study 3358 (Patient W and Patient X) and each of these patients discontinued the study. For 'Patient W' the event was recorded on Day 1 of Study 3358 and he was noted to have significant symptoms of withdrawal reflected in the SOWS score prior to actually receiving his first dose of Relistor in the study. Patient X was reported to have opioid withdrawal syndrome on Day 7. This patient did not appear to have any clinically significant change in either OOWS or SOWS scores following the first dose of Relistor. The maximum potential to experience a significant reversal of central analgesic effects or symptoms of opioid withdrawal would be anticipated to be present with the first dose of Relistor and not after multiple doses.

The other 2 patients experienced an AE of 'withdrawal syndrome' in Study 3358 (Patient Y [Day 44] and Patient Z [Day 1]). These events were non-serious AEs and resolved without recurrence during continued use of Relistor in the study. One (Patient Z) had no evidence of withdrawal based on SOWS and OOWS following the observed first dose and the other (Patient X) also had evidence of self-reported opioid withdrawal prior to the very first dose of Relistor and reported an improvement of symptoms 1 hour following Relistor dosing.

Table 27: SOWS and OOWS for Patients with Event of 'Withdrawal' in sNDA Studies

Patient ID	AE/ Study Day	SOWS (Study Day 1)		OOWS (Study Day 1)		Outcome
		Pre-Dose	1 Hour Post-Dose	Pre-Dose	1 Hour Post-Dose	
W	Drug Withdrawal Syndrome/ Day 1	32	44	2	7	Discontinued Study
X	Drug Withdrawal Syndrome/ Day 7	9	7	0	1	Discontinued Study
Y	Withdrawal Syndrome/ Day 44	14	9	0	0	Continued
Z	Withdrawal Syndrome/ Day 1	1	1	0	0	Continued

Abbreviations: SOWS = subjective opioid withdrawal scale; OOWS = objective opioid withdrawal scale; and AE =adverse event.

7.2.1 Analysis of Potential Withdrawal Symptoms in Patients with MACE

All 7 patients who were reported to have MACE (see Section 6.2) were evaluated for evidence or symptoms of opioid withdrawal around the time of their events.

Only 1 patient out of the 7 who were reported to have a MACE had concurrent symptoms which potentially were suggestive of opioid withdrawal. This subject ('Subject B' – see Table 19) experienced an MI on Day 6 and a concurrent SAE of coronary artery disease. Following the MI, the patient experienced congestive heart failure (Day 43) and worsening hypertension (Day 57). The patient underwent coronary artery bypass graft surgery (~ Study Day 75) and was maintained on Relistor through Study Day 274, when he discontinued due to relocation. This patient was advised to remain on Relistor by his cardiologist.

At his screening visit this patient was noted to have a BP of 170/80 mmHg and pulse of 64. On Study Day 1 his BP was 160/75 with a pulse of 62 before receiving Relistor and his BP was 160/74 with a pulse of 60 one hour following Relistor while reporting symptoms of hyperhidrosis, tremor and hot flush. The patient also experienced the same symptoms near the time of the MI and with the non-specific nature of these symptoms they may also have been consistent with his myocardial ischemia.

Based on all available information, none of the other 6 patients were reported to have any of the symptoms of interest (alone or in combination) at any time prior to or on the date of the event.

7.3 Potential Opioid Withdrawal Symptoms: Relistor vs. Opioid Labeling

Potential withdrawal symptoms observed in the Relistor OIC studies were consistent with frequency of the same symptoms observed in patients on chronic opioid therapy for chronic pain. Table 28 summarizes the incidence of withdrawal symptoms reported during open-label treatment in Relistor Studies 3356 and 3358 versus the labeling of extended-release opioids. As shown, the incidence of potential opioid withdrawal symptoms observed in the Relistor program is consistent with many opioid labels. Reasons for this include variations in the rate of opioid metabolism which may lead to a physiologic withdrawal if the opioid levels fall prior to the next

dose being given, as well as missed doses, dose titrations, variations in dose timing, and the practice of opioid rotation for patients on long-term opioid therapy. The selected symptoms occurred at equal or lower rates in the Relistor trials than they do in long-term opioid users. For example, anxiety, hot flush, and hyperhidrosis each occurred in 1% to 10% of patients in phase 2 and 3 studies of Embeda® (morphine sulfate and naltrexone hydrochloride). In the open-label phase of Study 3356, these AEs occurred in 0.3%, 1.4%, and 2.2% of Relistor patients, respectively, and in Study 3358, in 3.4%, 4.7%, and 9% of Relistor patients.

There was no apparent increase in the incidence or rate of withdrawal symptoms when Relistor treatment is added to continuing opioid therapy.

Table 28: Incidence of Potential Opioid Withdrawal Symptoms During Open-Label Treatment in Relistor Studies Compared to Approved, Extended-Release Opioids

Adverse Event	Relistor		Extended Release Opioids[1-6]
	8-wk Open-label Phase 3356 (N=364)	48-wk Open-label Study 3358 (N=1,034)	
Drug Withdrawal Syndrome	0	<0.4%	0-10%
Anxiety	0.3%	3.4%	0-10%
Hot Flush	1.4%	4.7%	0-10%
Hyperhidrosis	2.2%	9.0%	1-10%
Piloerection	0	0.5%	<1%
Tremor	0.8%	1.6%	0-10%

1. Exalgo (hydromorphone) Prescribing Information (2012). Mallinckrodt Brand Pharmaceuticals; Hazelwood, MO
2. Oxycontin (oxycodone) CR Prescribing Information (2012). Purdue Pharma L.P.; Stamford, CT
3. Opana ER (oxymorphone) Prescribing Information (2012). Endo Pharmaceuticals; Chadds Ford, PA
4. Avinza (morphine) Prescribing Information (2008). King Pharmaceuticals; Bristol, TN
5. Embeda (morphine/naltrexone) Prescribing Information (2009). King Pharmaceuticals; Bristol, TN
6. Nucynta ER (tapentadol) Prescribing Information (2012). Janssen Pharmaceuticals; Titusville, NJ

7.4 Summary of Opioid Withdrawal Scales

Data from validated withdrawal symptom scales utilized in the Relistor phase 3 studies for OIC in chronic NCP indicate that Relistor does not appear to be associated with higher rates of opioid withdrawal overall. As anticipated, most of the reported symptoms occurred following the first dose and the effects diminished over time.

The OOWS and SOWS are validated and reliable questionnaires that were developed primarily to assess opioid withdrawal that results from opioid abstinence in patients who are physically dependent on opioids (123). The OOWS is completed by a trained clinician, while the SOWS is completed by the patient. The OOWS evaluates 13 physically observable signs that are rated as present or absent by the rater: yawning, rhinorrhea, piloerection, perspiration, lacrimation,

tremor, mydriasis, hot/cold flush, restlessness, vomiting, muscle twitches, abdominal cramps, and anxiety. These symptoms are each scored 0 (not present) or 1 (present) for a maximum score of 13. The SOWS includes 16 items monitoring similar symptoms, with a maximum score of 64. Patients score each item according to the following scale: 0 (not at all), 1 (a little), 2 (moderately), 3 (quite a bit), and 4 (extremely).

In Study 3356, both scales were completed 3 times during the placebo-controlled period (Days 1, 14, and 28), and SOWS was measured 3 additional times during the open-label phase (Days 42, 56, and 84). In Study 3358, both scales were evaluated on Day 1 following the first dose of study drug. In each trial, the OOWS and SOWS were calculated both pre-dose (baseline) and approximately 1-hour post-dose on Day 1.

Study 3356 – Placebo-Controlled Analysis

Table 29 presents a summary of mean change from baseline through Day 28 in total OOWS and total SOWS scores, respectively, by treatment group in the double-blind period of Study 3356. As shown, clinician and patient ratings of opioid withdrawal symptoms did not show a clinically meaningful change or a trend suggestive of withdrawal in either scale for Relistor- or placebo-treated patients during double-blind treatment. Results were similar in analysis of SOWS total scores during 8 weeks of open-label Relistor treatment in Study 3356.

Table 29: Summary of Mean (SD) Change from Baseline in Opioid Withdrawal Scale Scores (OOWS and SOWS) During Double-Blind Treatment in Study 3356

	Relistor 12 mg QD (n=150)	Relistor 12 mg QOD (n=148)	Placebo (n=162)
Total OOWS Score, Mean (SD)			
Day 1	0.2 (0.7)	0.4 (1.5)	0.0 (0.5)
Day 14	0.1 (0.5)	0.0 (0.7)	0.0 (0.6)
Day 28	0.0 (0.7)	0.0 (0.6)	0.0 (0.6)
Total SOWS Score, Mean (SD)			
Day 1	-2.1 (7.6)	-1.5 (8.0)	-3.6 (6.2)
Day 14	-0.7 (9.0)	-0.4 (9.2)	-0.1 (7.8)
Day 28	-2.1 (9.0)	-0.3 (10.5)	-0.2 (7.9)

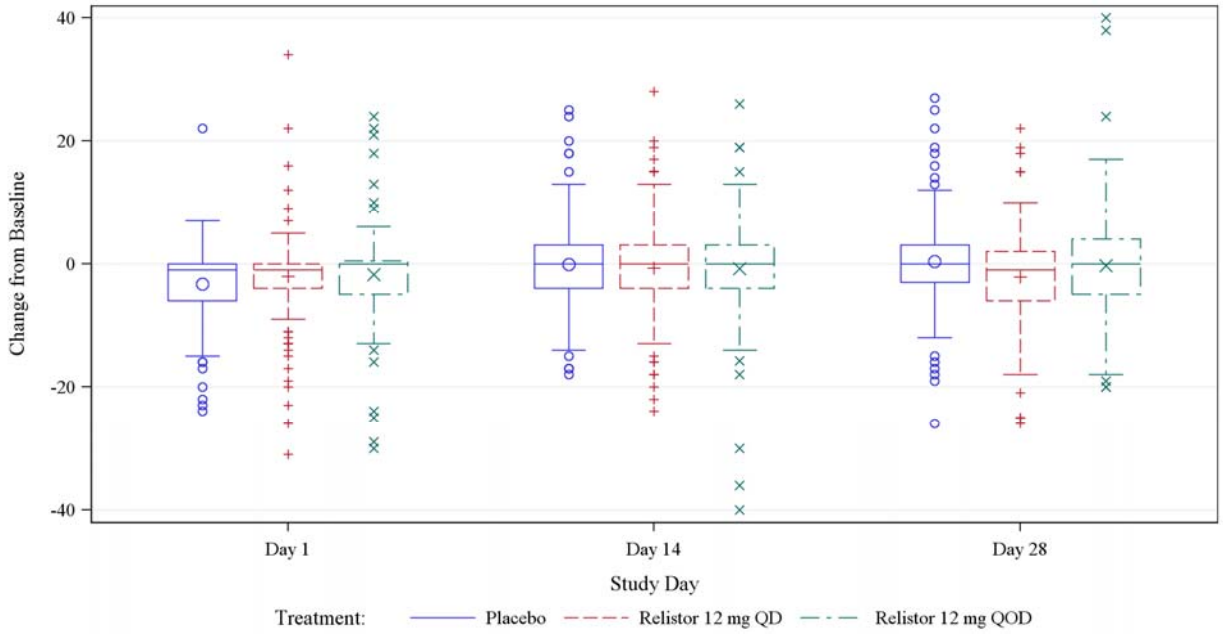
Abbreviations: OOWS =Objective Opioid Withdrawal Scale; SOWS = Subjective Opioid Withdrawal Scale; SD = standard deviation; QD = once daily; and QOD = once every other day.
Note: The OOWS evaluates 13 symptoms each scored 0 (not present) or 1 (present) for a maximum score of 13. The SOWS includes 16 items monitoring similar potential withdrawal symptoms. Each item is scored by the patient according to the following scale: 0 (not at all), 1 (a little), 2 (moderately), 3 (quite a bit), and 4 (extremely). The maximum SOWS score is 64.

Figure 15 presents a summary of change from baseline in SOWS total score (excluding abdominal cramping) by treatment group at Days 1, 14, and 28 in Study 3356. Each treatment group (placebo, Relistor 12 mg QD, and Relistor 12 mg QOD, respectively) is shown using a box plot, with the bottom and top of the box representing the first and third quartiles. The median

and mean are presented within each box, using a line and symbol, respectively. The whiskers (vertical lines above and below boxes) represent 1.5 times the interquartile range (distance between first and the third quartiles). Individual patient outliers are denoted with a symbol for each group outside of the whiskers.

Median and mean scores for each treatment group for change from baseline were near 0 at each time point during the study. The distribution of patients indicated that across placebo and Relistor groups, patients were just as likely or more likely to experience a decrease than an increase in SOWS score following dosing. There were no noticeable differences between the Relistor groups and the placebo group in trends at each time point, and the groups had similar numbers of outliers, both above and below the median.

Figure 15: Change from Baseline in SOWS Total Score (Excluding Cramping) by Treatment Group at Day 1, 14, and 28 –Study 3356



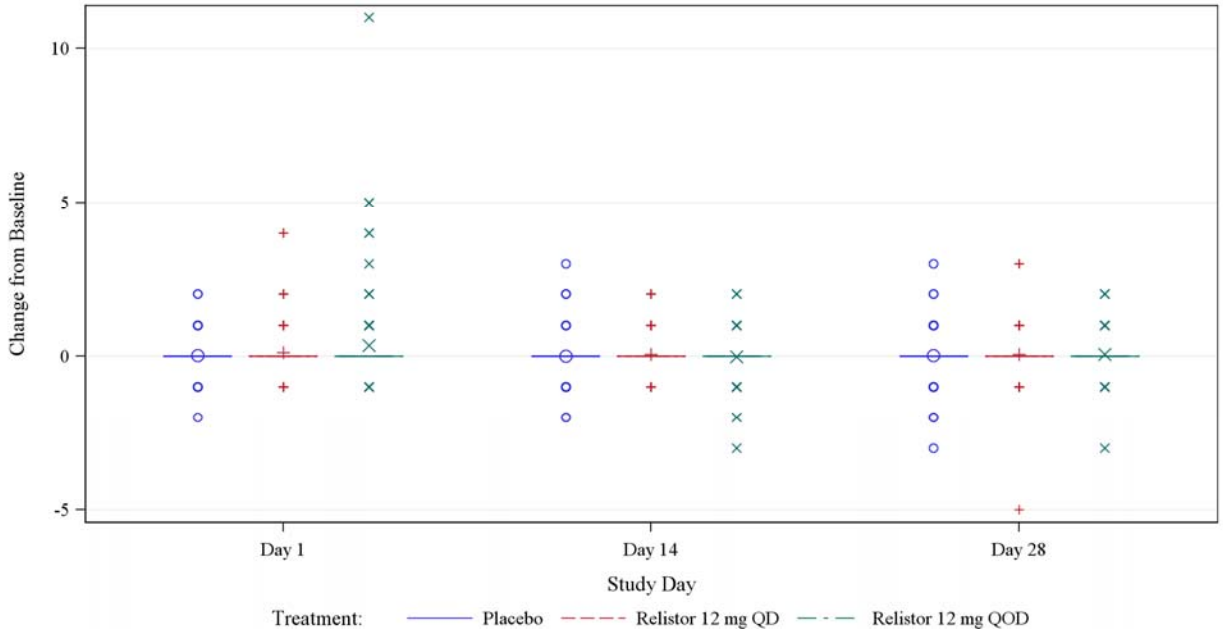
Abbreviations: SOWS = Subjective Opioid Withdrawal Scale.
Notes: Each treatment group (placebo, Relistor 12 mg QD, and Relistor 12 mg QOD, respectively) is shown for each Visit in Study 3356 during the double-blind period using box plots. The bottom and top of the box represent the first and third quartiles of patient data. The median and mean are presented within each box, using a line and symbol, respectively. The whiskers (vertical lines above and below boxes) represent 1.5 times the interquartile range (distance between first and the third quartiles). Individual patient outliers are denoted with a symbol for each group outside of the whiskers.

Figure 16 summarizes change from baseline in OOWS total score (excluding abdominal cramping) by treatment group at Days 1, 14, and 28 in Study 3356. Descriptions of data displays are the same as described above for the Figure 15 summary of SOWS data. However, in this figure, the box plots and whiskers for change from baseline are not visually discernable given that the vast majority of patients in each treatment group had no change from baseline in OOWS (i.e., change in OOWS score was 0) at each of these visits. There were no noticeable differences

between the Relistor groups and the placebo group in trends at each time point, and the groups had similar numbers of outliers, both above and below the median.

(Note: There was one outlier on Day 1 in a female patient who was taking methadone at a total morphine equivalent dose of 438 mg daily [see Day 1 of Figure 16]. Prior to her first dose of Relistor, she had an elevated SOWS score and had symptoms of hot flashes, muscle aching, muscle twitches, opioid craving, trouble sleeping and poor appetite. These symptoms persisted and she also developed several additional symptoms following dosing, including abdominal cramps and vomiting. All of her symptoms were reported as resolved on the same study day.)

Figure 16: Change from Baseline in OOWS Total Score (Excluding Cramping) by Treatment Group at Day 1, 14, and 28 – Study 3356



Abbreviations: OOWS = Objective Opioid Withdrawal Scale.
Notes: Each treatment group (placebo, Relistor 12 mg QD, and Relistor 12 mg QOD, respectively) is shown for each Visit in Study 3356 during the double-blind period using box plots. The bottom and top of the box represent the first and third quartiles of patient data. The median and mean are presented within each box, using a line and symbol, respectively. The whiskers (vertical lines above and below boxes) represent 1.5 times the interquartile range (distance between first and the third quartiles). Individual patient outliers are denoted with a symbol for each group outside of the whiskers.

7.5 Analysis of Pain Scores and Opioid Use in sNDA Studies

Overall, there were no notable effects on pain scores evaluated throughout the Relistor studies and no significant changes in the use of opioid analgesics. During double-blind treatment in Study 3356 there were no marked changes in the Relistor or placebo groups in the median or mean total daily opioid dose (by morphine equivalents) throughout the study. Table 30 displays summary statistics for the change from baseline in pain scores for Study 3356. The mean pain scores were similar in each treatment group and did not change from baseline to Day 14 or

Day 28. A similar lack of effect on pain scores was observed at each visit during open-label treatment in Studies 3356 and 3358.

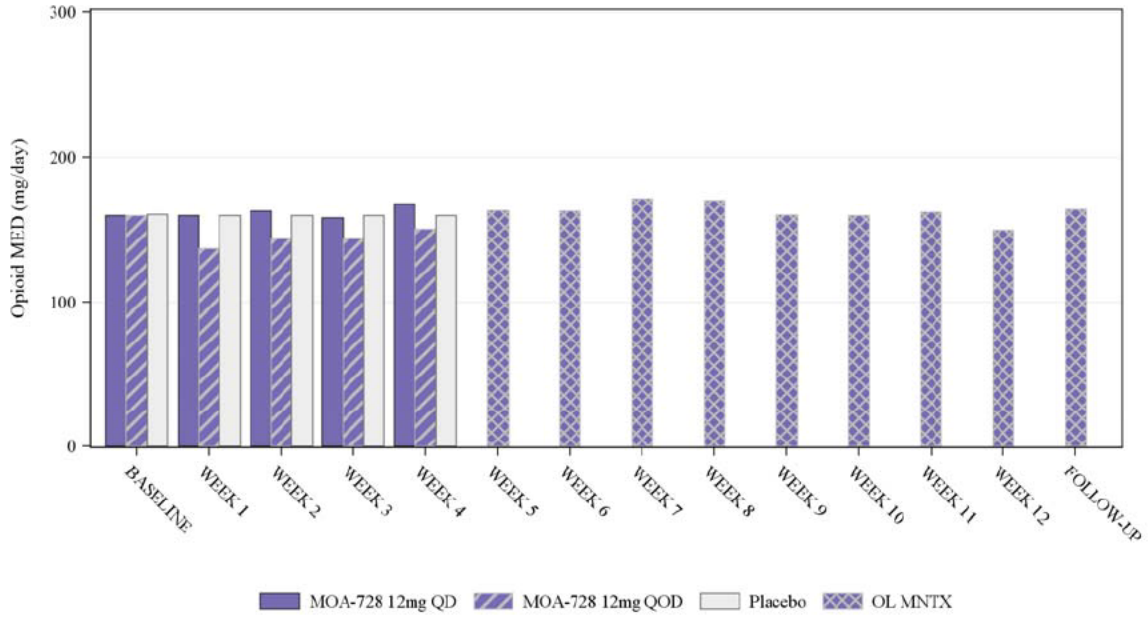
Table 30: Summary of Change from Baseline to Day 14 and Day 28 in Pain Scores - Placebo-Controlled Treatment Phase of Study 3356

Day	Treatment	N	Mean (SD)	Mean Change (SD)
Day 14	Relistor 12 mg QD	132	6.2 (1.9)	-0.0 (1.7)
	Relistor 12 mg QOD	132	6.1 (1.9)	-0.1 (1.5)
	Placebo	153	6.2 (2.0)	-0.1 (1.4)
Day 28	Relistor 12 mg QD	122	6.1 (1.9)	-0.2 (1.6)
	Relistor 12 mg QOD	120	5.9 (1.7)	-0.3 (1.5)
	Placebo	143	6.3 (2.0)	-0.1 (1.8)

Abbreviations: SD = standard deviation; QD = once daily; and QOD = once every other day.

Figure 17 presents a summary of change from baseline in median daily opioid use, expressed as oral morphine equivalents. Patients in the figure are summarized based on their randomized treatment group during the double-blind and open-label periods of the study. Note that patients randomized to placebo received blinded placebo for the first 4 weeks, and open-label Relistor treatment between Weeks 5 and 12. In general, daily opioid use was similar to baseline level in each of the treatment groups at each of the study time points. There were no marked changes from baseline in the median or mean opioid dose (by morphine equivalents).

Figure 17: Change from Baseline in Median Daily Oral Morphine Equivalent Dose by Randomized Treatment Group in Study 3356



Abbreviations: MOA or MNTX = Relistor; QD = once daily; and QOD = once every other day.

8.0 WORLDWIDE POSTMARKETING DATA: CV SAFETY AND WITHDRAWAL

Relistor is currently registered in 57 countries and marketed in 31 countries for the treatment of OIC in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. It is estimated that > 800,000 patients world-wide have been prescribed Relistor, representing more than 15,000 patient exposure years.

Post-marketing CV Events of Interest

As of May 01, 2014, the post-marketing surveillance database for Relistor includes 35 cases describing patients with fatal outcomes involving Relistor use. In total, 32 of the 35 deaths in the database describe non-CV events (e.g., progression of malignancy, sepsis, GI hemorrhage, unknown cause). Three (3) of the 35 case reports involve patients with CV-related events of interest (CVA, cardiac arrest, and cardiorespiratory arrest, respectively). In addition, 1 non-fatal MI has been reported during post-marketing surveillance. These 4 events are summarized below in Table 31.

Table 31: Potential MACE in Worldwide Relistor Postmarketing Database

Manufacturer Report No.	Reporter Type/Country	Age of Patient	MedDRA Preferred Term/Event Outcome
SP04011	Nurse/Finland	85	Acute Myocardial Infarction (non-fatal)
SP05466	Physician's Assistant/ USA	73	Cardiac Arrest (fatal)
SP03908	Nurse/France	55	Cardiorespiratory Arrest (fatal)
SP05771	Physician/USA	53	Cerebrovascular Accident (fatal)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities.
Search results reflect a data cut-off date of 01-Jan-2014.

Postmarketing Reports of Possible Opioid Withdrawal

The post-marketing Experience section of the current US Package Insert for Relistor® cites that "cases of opioid withdrawal have been reported," noting that this has been identified during post-approval use of Relistor, and because post-marketing events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

A search of the post-marketing safety database for Relistor identified 16 reports describing events of "withdrawal" or "reversal of opiate activity" in the setting of Relistor administration.

9.0 SUMMARY

There is an unmet need for effective therapies to treat OIC in patients with chronic NCP; particularly for patients who fail or are refractory to laxatives and other therapies. Peripheral mu opioid receptor antagonists are the only class of potential therapies that directly target the underlying effects of opioids on the GI tract. Relistor, as an example of this class of compounds, has demonstrated efficacy with a predictable and rapid response following dosing with an NNT of 2.5 to 5. Unique to Relistor is the ability to dose on a PRN basis with no apparent attenuation of efficacy over time.

Relistor is currently approved for the treatment of OIC in patients with advanced illness in over 30 countries and has never been removed from any country for safety reasons. Following receipt of a CRL for the expanded indication for SC Relistor to include patients with NCP, Salix appealed the decision to ODEIII. As a result, this advisory committee has been called to discuss the potential for a class CV effect and whether a premarket CVOT should be a requirement for this class of non-cardiac drugs.

The basis of the Division's concern for a potential signal and class effect was an observed imbalance in ischemic CV events, predominantly MIs, in a single study with a different compound (alvimopan; Study GSK014). The predicted distribution of 7 MI events in this placebo-controlled, 2:1 randomization study was 5 on active and 2 on placebo. In the study, however, all 7 events occurred in patients on alvimopan (32). The rate and timing of these events has never been replicated, either in other studies involving alvimopan or in any of the other OIC development programs for peripheral opioid receptor antagonists such as Relistor and naloxegol. A mechanism for the imbalance in MI events and subsequent event rate in the GSK014 study has not been identified. While this imbalance would appear to be a signal in the absence of other data at the time of FDA's review, the totality of the current data suggests that either some feature unique to that compound may have been responsible or that the imbalance may have been a chance occurrence.

No potential CV signal was observed in the Relistor clinical trials dataset, which includes > 6000 subjects or in the Relistor post-marketing experience, which includes > 800,000 patient exposures representing more than 15,000 person years of exposure. Further the rate of MACE in the long-term safety trial for Relistor (Study 3358) is interpretable as it is consistent both with epidemiologic studies of similar NCP populations as well as that observed in the randomized long-term safety study of naloxegol in NCP patients. While Relistor and alvimopan share a therapeutic mechanism of action for OIC, these drugs are unrelated in chemical structure and have differential pharmacology that results in differences in dosing, dosing frequency, and efficacy. Relistor is in the subclass of mu opioid antagonists derived from morphine, whereas alvimopan is derived from meperidine, a synthetic opioid that has been associated with CV risk factors (36;37).

Following receipt of the CRL, Salix met with DGIEP for an End-of-Review meeting as well as with the FDA during a Formal Appeal Meeting. During these meetings, Salix raised a number of

concerns around the conduct and particularly the interpretability of a CVOT for mu opioid receptor antagonists in OIC. There are considerable issues surrounding variable periods on and off drug with PRN dosing specific to a drug like Relistor which is used to treat a side effect from another drug. Relistor is being used only to ameliorate the side effect of OIC in a patient taking chronic opioids. There is no incentive for a patient to inject themselves with blinded study medication every day unless they are receiving benefit. Experience in this therapeutic area has predicted that such a trial will quickly be met with both compliance and patient attrition issues, such as that observed in GSK014. Patient retention and compliance issues would need to be addressed at the outset of the trial.

During the End of Review and appeal meeting with DGIEP and the FDA, Salix raised a number of these concerns, which included:

- Population enrichment is difficult because recruitment of high risk patients (e.g., recent acute coronary syndrome) on chronic opioids who have OIC and are willing to enroll into a 1-2 year study with a product that requires self-administered SC injections would be challenging. While enrollment of high risk CV patients theoretically could reduce sample size, such a population would be extremely difficult to identify and enroll. Selecting such a population would also impact the ability to generalize results to the NCP population.
- Relistor works within minutes to hours and has a NNT of 2.5 to 5. With such a rapid and high rate of response, non-responding patients could quickly become discouraged and seek alternative therapy. At the investigative site level, this could compromise the ability to maintain the study blind.
- NCP patients switch, change, and/or stop their opioids. Given that Relistor is only useful for OIC, it is unclear how best to handle patients who no longer need to take Relistor or opioids.
- Relistor is approved and could be obtained (albeit, off label) by non-responding placebo patients seeking relief for OIC. This could happen during study participation or after early withdrawal from the study.
- Study 3358 demonstrates that long term Relistor use often results in less than everyday use. In a long-term CVOT, where patients would be taking daily SC injections for 1 or more years, we may end up with data very similar to Study 3358 where 5 of the 7 cases of unadjudicated MACE were actually off drug for 2 days or longer. Interpretation of off drug events with a product that so rapidly enters and exits the body is difficult.

Each of these issues alone or in combination could complicate the interpretability of study results and affect the ability to enroll and complete the study. Further, the low MACE event rate in chronic pain patients with OIC also suggests a very large sample size for a CVOT, potentially tens of thousands of patients for each sponsor.

Relistor® is currently approved and available for OIC in 31 countries and continues to meet the previously unmet need of treating OIC in very sick patients with advanced illness. Relistor's

efficacy and safety in OIC patients with advanced illness and NCP is supported by the totality of Relistor data from > 150 nonclinical studies and 65 clinical studies (phases 1-4), as well as extensive worldwide postmarketing use. It is the entirety of this experience that gives us great confidence in the efficacy and safety of Relistor in meeting the unmet need in the NCP population.

Salix has a responsibility to the patients we serve to perform careful post marketing surveillance when a product is approved, whether that approval is as an NDA or a sNDA. As part of that responsibility, Salix is committed to exploring useful measures of safety that allow for reasonable signal detection and interpretation.

In the case of SC Relistor, an approved product administered as a SC injection on a PRN basis for relief from a symptom of another prescription medication, the conduct of a CVOT runs a very high risk of operational and interpretation failure. The possibility of recruiting, retaining, and maintaining compliance through the trial is very unlikely. Even if it is completed, the biggest challenge may be in understanding and interpreting the results.

Post-marketing studies may be an alternative path to monitor for potential signals in situations where products are undergoing a label expansion. There may be an opportunity to combine different approaches and databases to more accurately and robustly assess CV events.

10.0 APPENDICES

10.1 RELISTOR® Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RELISTOR safely and effectively. See full prescribing information for RELISTOR.

RELISTOR (methylnaltrexone bromide) Subcutaneous Injection
Initial U.S. Approval: 2008

RECENT MAJOR CHANGES

General Dosing Information *(2.1)*	[08/2013]
Dosing *(2.2)*	[08/2013]
Use in Patients with Severe Renal Impairment *(2.3)*	[08/2013]
Administration and Storage *(2.4)*	[08/2013]
Gastrointestinal Perforation *(5.1)*	[08/2013]
Severe or Persistent Diarrhea *(5.2)*	[08/2013]

INDICATIONS AND USAGE

RELISTOR is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied. (*1*)

DOSAGE AND ADMINISTRATION

RELISTOR is administered as a subcutaneous injection. The usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period. (*2.2*)

The recommended dose of RELISTOR is 8 mg for patients weighing 38 to less than 62 kg or 12 mg for patients weighing 62 to 114 kg. Patients whose weights fall outside of these ranges should be dosed at 0.15 mg/kg. See the table below to determine the correct injection volume. (*2.2*)

Patient Weight	Injection Volume	Dose
Less than 38 kg	**See below***	0.15 mg/kg
38 kg to less than 62 kg	**0.4 mL**	8 mg
62 kg to 114 kg	**0.6 mL**	12 mg
More than 114 kg	**See below***	0.15 mg/kg

* The injection volume for these patients should be calculated using one of the following (*2.2*):

- Multiply the patient weight in kilograms by 0.0075 and round up the volume to the nearest 0.1 mL.

Only patients requiring an 8 mg or 12 mg dose should be prescribed pre-filled syringes (*2.2, 3*).

In patients with severe renal impairment (creatinine clearance less than 30 mL/min), dose reductions of RELISTOR by one half is recommended. *(8.6)*

DOSAGE FORMS AND STRENGTHS

RELISTOR is available in the following dosage forms:

- Single-use vial containing 12 mg/0.6 mL solution for subcutaneous injection, for use with a 27 gauge x ½-inch needle and 1 mL syringe
- Single-use vial containing 12 mg/0.6 mL solution for subcutaneous injection with one 1 mL syringe with retractable 27 gauge x ½-inch needle, two alcohol swabs.
- Single-use pre-filled syringe containing 8 mg/0.4 mL solution for subcutaneous injection.
- Single-use pre-filled syringe containing 12 mg/0.6 mL solution for subcutaneous injection.

CONTRAINDICATIONS

- RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. (*4*)

WARNINGS AND PRECAUTIONS

- Rare cases of gastrointestinal (GI) perforation have been reported in advanced illness patients. Use RELISTOR with caution in patients with known or suspected lesions of the GI tract. (*5.1*)
- If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician. (*5.2*)

ADVERSE REACTIONS

The most common (≥5%) adverse reactions reported with RELISTOR are abdominal pain, flatulence, nausea, dizziness, diarrhea and hyperhidrosis. (*6.1*)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals Inc. at 1-800-508-0024 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

In an *in vivo* study Relistor did not significantly affect the metabolism of the CYP2D6 substrate, dextromethorphan. In vitro methylnaltrexone did not significantly inhibit or induce cytochrome P450 (CYP) isozymes including CYP 1A2, 2A6, 2B6, 2C9, 2C19, or 3A4 (*7.1*)

USE IN SPECIFIC POPULATIONS

Pediatric Use: Safety and efficacy of RELISTOR have not been established in pediatric patients. (*8.4*)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 08/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RELISTOR® is indicated for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

Limitation of use: Use of RELISTOR beyond four months has not been studied in the advanced illness population.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

RELISTOR is for subcutaneous use only.

2.2 Dosing

For adult patients with opioid-induced constipation and advanced illness, the usual schedule is one dose every other day, as needed, but no more frequently than one dose in a 24-hour period [*see Clinical Studies (14)*].

The recommended dose of RELISTOR is 8 mg subcutaneously for opioid-induced constipation and advanced illness adult patients weighing 38 kg to less than 62 kg or 12 mg subcutaneously for patients weighing 62 kg to 114 kg. Adult patients whose weight falls outside of these ranges should be dosed at 0.15 mg/kg. See Table 1 to determine the correct injection volume. The pre-filled syringe is designed to deliver a fixed dose; therefore, adult patients requiring dosing calculated on a mg/kg basis should not be prescribed pre-filled syringes.

Table 1: Weight of Adult Patient with Opioid-Induced Constipation and Advanced Illness	**Injection Volume**	**Subcutaneous Dose**
Less than 38 kg	**See below***	0.15 mg/kg
38 kg to less than 62 kg	**0.4 mL**	8 mg
62 kg to 114 kg	**0.6 mL**	12 mg
More than 114 kg	**See below***	0.15 mg/kg

* The injection volume for these patients should be calculated using the following method:

Multiply the patient weight in kilograms by 0.0075 and round up the volume to the nearest 0.1 mL.

2.3 Use in Patients with Severe Renal Impairment

In adult patients with severe renal impairment (creatinine clearance less than 30 mL/min as estimated by Cockcroft-Gault), dose reduction of RELISTOR by one-half is recommended [*see*

Use in Specific Populations (8.6)]. No dosage adjustment is recommended for adult patients with mild to moderate renal impairment.

The pre-filled syringe is designed to deliver a fixed dose; therefore, adult patients with severe renal impairment should only be prescribed single-use vials to ensure correct dosing.

2.4 Administration and Storage

RELISTOR is a sterile, clear, and colorless to pale yellow aqueous solution. Inspect parenteral drug product visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the vial if any of these are present.

Inject RELISTOR subcutaneously in the upper arm, abdomen or thigh. Do not inject at the same spot each time (rotate injection sites).

Single-use Vials

Once drawn into the 1 mL syringe with a 27-gauge x ½-inch needle, if immediate administration is not possible, store at ambient room temperature and administer within 24 hours. Discard any unused portion that remains in the vial. Advise patients concerning proper training in subcutaneous technique.

Single-use Pre-filled Syringes

Only adult patients requiring an 8 mg or 12 mg dose should be prescribed pre-filled syringes. Do not remove the pre-filled syringe from the tray until ready to administer.

3 DOSAGE FORMS AND STRENGTHS

- Single-use vial containing 12 mg/0.6 mL solution for subcutaneous injection, for use with a 27 gauge x ½-inch needle and 1 mL syringe
- Single-use vial containing 12 mg/0.6 mL solution for subcutaneous injection, with one 1 mL syringe with retractable 27 gauge x ½-inch needle, two alcohol swabs
- Single-use pre-filled syringe containing 8 mg/0.4 mL solution for subcutaneous injection, with a 29-gauge x ½-inch fixed needle and a needle guard
- Single-use pre-filled syringe containing 12 mg/0.6 mL solution for subcutaneous injection, with a 29-gauge x ½-inch fixed needle and a needle guard

4 CONTRAINDICATIONS

RELISTOR is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforation

Cases of gastrointestinal (GI) perforation have been reported in adult patients with opioid-induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract (i.e., cancer, peptic ulcer, Ogilvie's syndrome). Perforations have involved varying regions of the GI tract (e.g., stomach, duodenum, or colon).

Use RELISTOR with caution in patients with known or suspected lesions of the GI tract. Advise patients to discontinue therapy with RELISTOR and promptly notify their physician if they develop severe, persistent, or worsening abdominal symptoms.

5.2 Severe or Persistent Diarrhea

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of RELISTOR was evaluated in two, double-blind, placebo-controlled trials in patients with advanced illness receiving palliative care: Study 1 included a single-dose, double-blind, placebo-controlled period, whereas Study 2 included a 14-day multiple dose, double-blind, placebo-controlled period [see *Clinical Studies (14)*]. The majority of patients had a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Patients were receiving opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg), and had opioid-induced constipation (either <3 bowel movements in the preceding week or no bowel movement for 2 days). Both the methylnaltrexone bromide and placebo patients were on a stable laxative regimen for at least 3 days prior to study entry and continued on their regimen throughout the study.

The most common (≥5%) adverse reactions in patients receiving RELISTOR are shown in Table 2 below.

Table 2
Adverse Reactions from all Doses in Double-Blind, Placebo-Controlled Clinical Studies of RELISTOR in Adult Patients with Opioid-Induced Constipation and Advanced Illness*

Adverse Reaction	RELISTOR N = 165	Placebo N = 123
Abdominal Pain	47 (28.5%)	12 (9.8%)
Flatulence	22 (13.3%)	7 (5.7%)
Nausea	19 (11.5%)	6 (4.9%)
Dizziness	12 (7.3%)	3 (2.4%)
Diarrhea	9 (5.5%)	3 (2.4%)
Hyperhidrosis	11 (6.7%)	8 (6.5%)

* Doses: 0.075, 0.15, and 0.30 mg/kg/dose

The rates of discontinuation due to adverse events during the double-blind placebo controlled clinical trials (Study 1 and Study 2) were comparable between RELISTOR (1.2%) and placebo (2.4%).

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of RELISTOR. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting or causal connection to RELISTOR, or a combination of these factors.

Gastrointestinal

Perforation, cramping, vomiting

General Disorders and Administrative Site Disorders

Diaphoresis, flushing, malaise, pain. Cases of opioid withdrawal have been reported.

7 DRUG INTERACTIONS

7.1 Drugs Metabolized by Cytochrome P450 Isozymes

In healthy subjects, a subcutaneous dose of 0.30 mg/kg of methylnaltrexone did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

In vitro methylnaltrexone did not significantly inhibit or induce the activity of cytochrome P450 (CYP) isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, or CYP3A4.

In vitro, methylnaltrexone did not induce the enzymatic activity of CYP2E1.

7.2 Drugs Renally Excreted

Methylnaltrexone is actively secreted in the kidney. The potential of drug interactions between methylnaltrexone bromide and other drugs that are inhibitors of transporters in the kidney has not been fully investigated *[see Pharmacokinetics (12.3)]*.

7.3 Cimetidine

Cimetidine given 400 mg three times daily did not significantly affect the systemic exposure to methylnaltrexone. The effect of a higher cimetidine dose (e.g., 800 mg) on the systemic exposure of methylnaltrexone has not been evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Reproduction studies have been performed in pregnant rats at intravenous doses up to about 14 times the recommended maximum human subcutaneous dose of 0.3 mg/kg based on the body surface area and in pregnant rabbits at intravenous doses up to about 17 times the recommended maximum human subcutaneous dose based on the body surface area and have revealed no evidence of impaired fertility or harm to the fetus due to methylnaltrexone bromide. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, methylnaltrexone bromide should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

Effects of RELISTOR on mother, fetus, duration of labor, and delivery are unknown. There were no effects on the mother, labor, delivery, or on offspring survival and growth in rats following subcutaneous injection of methylnaltrexone bromide at dosages up to 25 mg/kg/day.

8.3 Nursing Mothers

Results from an animal study using [^{3}H]-labeled methylnaltrexone bromide indicate that methylnaltrexone bromide is excreted via the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RELISTOR is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of RELISTOR have not been established in pediatric patients.

8.5 Geriatric Use

In the phase 2 and 3 double-blind studies, a total of 77 (24%) patients aged 65-74 years (54 methylnaltrexone bromide, 23 placebo) and a total of 100 (31.2%) patients aged 75 years or older (61 methylnaltrexone bromide, 39 placebo) were enrolled. Pharmacokinetics of methylnaltrexone was similar between the elderly (mean age 72 years old) and young adults (mean age 30 years old). No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Based on pharmacokinetic data, and safety and efficacy data from controlled clinical trials, no dose adjustment based on age is recommended.

8.6 Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Dose-reduction by one half is recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min as estimated by Cockcroft-Gault).

In a study of volunteers with varying degrees of renal impairment receiving a single dose of 0.30 mg/kg methylnaltrexone bromide, renal impairment had a marked effect on the renal excretion of methylnaltrexone bromide. Severe renal impairment decreased the renal clearance of methylnaltrexone bromide by 8- to 9-fold and resulted in a 2-fold increase in total methylnaltrexone bromide exposure (AUC). C_{max} was not significantly changed. No studies were performed in patients with end-stage renal impairment requiring dialysis.

8.7 Hepatic Impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of methylnaltrexone has not been studied.

10 OVERDOSAGE

During clinical trials of RELISTOR administered subcutaneously, no cases of methylnaltrexone bromide overdose were reported. A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus.

Signs or symptoms of orthostatic hypotension should be monitored, and treatment should be initiated, as appropriate.

11 DESCRIPTION

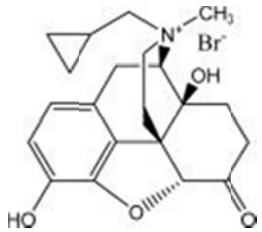
RELISTOR (methylnaltrexone bromide) injection, a peripherally-acting mu-opioid receptor antagonist, is a sterile, clear and colorless to pale yellow aqueous solution. The chemical name for methylnaltrexone bromide is (*R*)-*N*-(cyclopropylmethyl) noroxymorphone methobromide. The molecular formula is $C_{21}H_{26}NO_4Br$, and the molecular weight is 436.36.

Each 3 mL vial contains 12 mg of methylnaltrexone bromide in 0.6 mL of water. The excipients are 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride. During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

Each 8 mg/0.4 mL pre-filled syringe (1 mL syringe) contains 8 mg of methylnaltrexone bromide in 0.4 mL of water. The excipients are 2.6 mg sodium chloride USP, 0.16 mg edetate calcium disodium USP, and 0.12 mg glycine hydrochloride.

Each 12 mg/0.6 mL pre-filled syringe (1 mL syringe) contains 12 mg of methylnaltrexone bromide in 0.6 mL of water. The excipients are 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride.

The structural formula is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylnaltrexone is a selective antagonist of opioid binding at the mu-opioid receptor. As a quaternary amine, the ability of methylnaltrexone to cross the blood-brain barrier is restricted. This allows methylnaltrexone to function as a peripherally-acting mu-opioid receptor antagonist in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.

12.2 Pharmacodynamics

Effect on Cardiac Repolarization

In a randomized, double-blind placebo- and (open-label) moxifloxacin-controlled 4-period crossover study, 56 healthy subjects were administered methylnaltrexone bromide 0.3 mg/kg and methylnaltrexone bromide 0.64 mg/kg by intravenous infusion over 20 minutes, placebo, and a single oral dose of moxifloxacin. At both the 0.3 mg/kg and 0.64 mg/kg methylnaltrexone bromide doses, no significant effect on the QTc interval was detected.

12.3 Pharmacokinetics

Absorption

Following subcutaneous administration, methylnaltrexone achieved peak concentrations (C_{max}) at approximately 0.5 hours. Across the range of doses from 0.15 mg/kg to 0.50 mg/kg, mean C_{max} and area under the plasma concentration-time curve (AUC) increased in a dose-proportional

manner. There was no accumulation of methylnaltrexone following once-daily subcutaneous dosing of methylnaltrexone bromide 12 mg for seven consecutive days in healthy subjects.

Table 3: Pharmacokinetic Parameters of Methylnaltrexone Following Subcutaneous Doses

Parameter	0.15 mg/kg single dose	12 mg single dose	12 mg at steady-state
C_{max} (ng/mL) [i)]	117 (32.7)	140 (35.6)	119 (27.2)
t_{max} (hr) [ii)]	0.5 (0.25-0.75)	0.25 (0.25-0.5)	0.25 (0.25-0.5)
AUC_{24} (ng·hr/mL) [i)]	175 (36.6)	218 (28.3)	223 (28.2)

i) Expressed as mean (SD).
ii) Expressed as median (range).

Distribution

The steady-state volume of distribution (Vss) of methylnaltrexone is approximately 1.1 L/kg. The fraction of methylnaltrexone bound to human plasma proteins is 11.0% to 15.3%, as determined by equilibrium dialysis.

Metabolism

In a mass balance study, approximately 44% of the administered radioactivity was recovered in the urine over 24 hours with 5 distinct metabolites and none of the detected metabolites was in amounts over 6% of administered radioactivity. Conversion to methyl-6-naltrexol isomers (5% of total) and methylnaltrexone sulfate (1.3% of total) appear to be the primary pathways of metabolism. N-demethylation of methylnaltrexone to produce naltrexone is not significant.

After 12 mg once daily dosing the mean AUC_{0-24} ratio of metabolites to methylnaltrexone at steady-state was 30%, 19%, and 9% for methylnaltrexone sulfate, methyl-6α-naltrexol, and methyl-6β-naltrexol, respectively. Methyl-6α-naltrexol, and methyl-6β-naltrexol were active mu-opioid receptor antagonists and methylnaltrexone sulfate is a weak mu-opioid receptor antagonist.

Methylnaltrexone is conjugated by sulfotransferase SULT1E1 and SULT2A1 isoforms to methylnaltrexone sulfate. Conversion to methyl-6-naltrexol isomers is mediated by aldo-keto reductase 1C enzymes.

Excretion

After intravenous administration, approximately half of the dose was excreted in the urine (53.6%) and 17.3% of administered dose was excreted in the feces up to 168 hours postdose. Methylnaltrexone is excreted primarily as the unchanged drug in the urine and feces. The terminal half-life ($t_{1/2}$) is approximately 8 hours. Active renal secretion of methylnaltrexone is

suggested by renal clearance of methylnaltrexone that is approximately 4-5 fold higher than creatinine clearance.

Specific Populations

Geriatric

A study was conducted to characterize the pharmacokinetics of methylnaltrexone after single dose of 24 mg methylnaltrexone via intravenous infusion over 20 min in healthy adults between 18 and 45 years of age and in healthy adults aged 65 years and older. In elderly subjects, mean clearance was about 20% lower (56 L/h versus 70 L/h) and AUC_{∞} was 26% higher than in subjects between 18 and 45 years of age.

Renal impairment

In a study of volunteers with varying degrees of renal impairment receiving a single dose of 0.30 mg/kg methylnaltrexone bromide, renal impairment had a marked effect on the renal excretion of methylnaltrexone. Severe renal impairment decreased the renal clearance of methylnaltrexone by 8- to 9-fold and resulted in a 2-fold increase in total methylnaltrexone exposure (AUC). Mean C_{max} was not significantly changed.

Hepatic impairment

The effect of mild and moderate hepatic impairment on the systemic exposure to methylnaltrexone has been studied in 8 subjects each, with Child-Pugh Class A and B, compared to healthy subjects. Results showed no meaningful effect of hepatic impairment on the AUC or C_{max} of methylnaltrexone.

Drug Interactions

In vitro studies suggested that methylnaltrexone was a substrate of Organic Cation Transporter 1 but not a substrate of Organic Anion Transporter 1 or of P-glycoprotein.

Cimetidine

A clinical drug interaction study in healthy adult subjects evaluated the effects of cimetidine, a drug that inhibits the active renal secretion of organic cations, on the pharmacokinetics of methylnaltrexone (24 mg administered as an IV infusion over 20 minutes). A single dose of methylnaltrexone was administered before cimetidine dosing and with the last dose of cimetidine (400 mg every 8 hours for 6 days). Mean C_{max} and AUC of methylnaltrexone increased by 10% with concomitant cimetidine administration. The renal clearance of methylnaltrexone decreased about 40%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year oral carcinogenicity studies have been conducted with methylnaltrexone in CD-1 mice at doses up to 200 mg/kg/day (about 108 times the recommended human dose of 0.15 mg/kg

based on body surface area) in males and 400 mg/kg/day (about 216 times the recommended human dose of 0.15 mg/kg based on body surface area) in females and in Sprague Dawley rats at oral doses up to 300 mg/kg/day (about 324 times the recommended human dose of 0.15 mg/kg based on body surface area). Oral administration of methylnaltrexone for 104 weeks did not produce tumors in mice and rats.

Mutagenesis

Methylnaltrexone bromide was negative in the Ames test, chromosome aberration tests in Chinese hamster ovary cells and human lymphocytes, in the mouse lymphoma cell forward mutation tests and in the *in vivo* mouse micronucleus test.

Impairment of Fertility

Methylnaltrexone bromide at subcutaneous doses up to 150 mg/kg/day (about 81 times the recommended maximum human subcutaneous dose based on the body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

13.2 Animal Toxicology and/or Pharmacology

In an *in vitro* human cardiac potassium ion channel (hERG) assay, methylnaltrexone bromide caused concentration-dependent inhibition of hERG current (1%, 12%, 13% and 40% inhibition at 30, 100, 300 and 1000 μM concentrations, respectively). Methylnaltrexone bromide had a hERG IC_{50} of > 1000 μM. In isolated dog Purkinje fibers, methylnaltrexone bromide caused prolongations in action potential duration (APD). The highest tested concentration (10 μM) in the dog Purkinje fiber study was about 18 and 37 times the C_{max} at human subcutaneous (SC) doses of 0.3 and 0.15 mg/kg, respectively. In isolated rabbit Purkinje fibers, methylnaltrexone bromide (up to 100 μM) did not have an effect on APD, compared to vehicle control. The highest methylnaltrexone bromide concentration (100 μM) tested was about 186 and 373 times the human C_{max} at SC doses of 0.3 and 0.15 mg/kg, respectively. In anesthetized dogs, methylnaltrexone bromide caused decreases in blood pressure, heart rate, cardiac output, left ventricular pressure, left ventricular end diastolic pressure, and +dP/dt at ≥ 1 mg/kg. In conscious dogs, methylnaltrexone bromide caused a dose-related increase in QTc interval. After a single intravenous dosage of 20 mg/kg to beagle dogs, predicted C_{max} and AUC values were approximately 482 and 144 times, respectively, the exposure at human SC dose of 0.15 mg/kg and 241 times and 66 times, respectively, the exposure at a human SC dose of 0.3 mg/kg. In conscious guinea pigs, methylnaltrexone caused mild prolongation of QTc (4% over baseline) at 20 mg/kg, intravenous. A thorough QTc assessment was conducted in humans [*see Clinical Pharmacology (12.2)*].

In juvenile rats administered intravenous methylnaltrexone bromide for 13 weeks, adverse clinical signs such as convulsions, tremors and labored breathing occurred at dosages of 3 and 10 mg/kg/day (about 3.2 and 11 times, respectively, the recommended human dose of 0.15 mg/kg based on the body surface area). Similar adverse clinical signs were seen in adult rats at 20 mg/kg/day (about 22 times the recommended human dose of 0.15 mg/kg based on the body surface area). Juvenile rats were found to be more sensitive to the toxicity of methylnaltrexone bromide when compared to adults. The no observed adverse effect levels (NOAELs) in juvenile

and adult rats were 1 and 5 mg/kg/day, respectively (about 1.1 and 5.4 times respectively, the recommended human dose of 0.15 mg/kg based on the body surface area).

In juvenile dogs administered intravenous methylnaltrexone bromide for 13 weeks, juvenile dogs had a toxicity profile similar to adult dogs. Following intravenous administration of methylnaltrexone bromide for 13 weeks, decreased heart rate (13.2 % reduction compared to pre-dose) in juvenile dogs and prolonged QTc interval in juvenile (9.6% compared to control) and adult (up to 15% compared to control) dogs occurred at 20 mg/kg/day (about 72 times the recommended human subcutaneous doses of 0.15 mg/kg based on the body surface area). Clinical signs consistent with effects on the CNS (including tremors and decreased activity) occurred in both juvenile and adult dogs. The NOAELs in juvenile and adult dogs were 5 mg/kg/day (about 18 times the recommended human subcutaneous doses of 0.15 mg/kg based on the body surface area).

14 CLINICAL STUDIES

The efficacy and safety of RELISTOR in the treatment of opioid-induced constipation in advanced illness patients receiving palliative care was demonstrated in two randomized, double-blind, placebo-controlled studies. In these studies, the median age was 68 years (range 21-100); 51% were females. The majority of patients had a primary diagnosis of incurable cancer; other primary diagnoses included end-stage COPD/emphysema, cardiovascular disease/heart failure, Alzheimer's disease/dementia, HIV/AIDS, or other advanced illnesses. Prior to screening, patients had been receiving palliative opioid therapy (median daily baseline oral morphine equivalent dose = 172 mg), and had opioid-induced constipation (either <3 bowel movements in the preceding week or no bowel movement for >2 days). Patients were on a stable opioid regimen ≥ 3 days prior to randomization (not including PRN or rescue pain medication) and received their opioid medication during the study as clinically needed. Patients maintained their regular laxative regimen for at least 3 days prior to study entry, and throughout the study. Rescue laxatives were prohibited from 4 hours before to 4 hours after taking an injection of study medication.

Study 1 compared a single, double-blind, subcutaneous dose of RELISTOR 0.15 mg/kg, or RELISTOR 0.3 mg/kg versus placebo. The double-blind dose was followed by an open-label 4-week dosing period, where RELISTOR could be used as needed, no more frequently than 1 dose in a 24 hour period. Throughout both study periods, patients maintained their regular laxative regimen. A total of 154 patients (47 RELISTOR 0.15 mg/kg, 55 RELISTOR 0.3 mg/kg, 52 placebo) were enrolled and treated in the double-blind period. The primary endpoint was the proportion of patients with a rescue-free laxation within 4 hours of the double-blind dose of study medication. RELISTOR-treated patients had a significantly higher rate of laxation within 4 hours of the double-blind dose (62% for 0.15 mg/kg and 58% for 0.3 mg/kg) than did placebo-treated patients (14%); $p < 0.0001$ for each dose versus placebo (Figure 1).

Study 2 compared double-blind, subcutaneous doses of RELISTOR given every other day for 2 weeks versus placebo. Patients received opioid medication ≥ 2 weeks prior to receiving study medication. During the first week (days 1, 3, 5, 7) patients received either 0.15 mg/kg RELISTOR or placebo. In the second week the patient's assigned dose could be increased to 0.30 mg/kg if the patient had 2 or fewer rescue-free laxations up to day 8. At any time, the

patient's assigned dose could be reduced based on tolerability. Data from 133 (62 RELISTOR, 71 placebo) patients were analyzed. There were 2 primary endpoints: proportion of patients with a rescue-free laxation within 4 hours of the first dose of study medication and proportion of patients with a rescue-free laxation within 4 hours after at least 2 of the first 4 doses of study medication. RELISTOR-treated patients had a higher rate of laxation within 4 hours of the first dose (48%) than placebo-treated patients (16%); $p < 0.0001$ (Figure 1). RELISTOR-treated patients also had significantly higher rates of laxation within 4 hours after at least 2 of the first 4 doses (52%) than did placebo-treated patients (9%); $p < 0.0001$. In both studies, in approximately 30% of patients, laxation was reported within 30 minutes of a dose of RELISTOR.

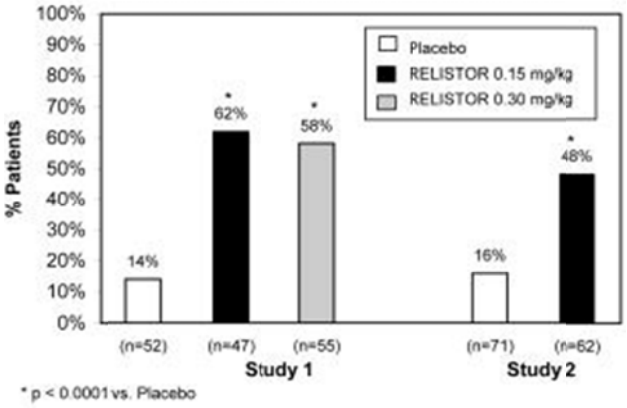


Figure 1. Laxation Response Within 4 Hours of the First Dose

In both studies, there was no evidence of differential effects of age or gender on safety or efficacy. No meaningful subgroup analysis could be conducted on race because the study population was predominantly Caucasian (88%).

Durability of Response

Durability of response was explored in Study 2 and the laxation response rate was consistent from dose 1 through dose 7 over the course of the 2-week, double-blind period.

The efficacy and safety of methylnaltrexone bromide was also demonstrated in open-label treatment administered from Day 2 through Week 4 in Study 1, and in two open-label extension studies (Study 1EXT and Study 2EXT) in which RELISTOR was given as needed for up to 4 months. During open-label treatment, patients maintained their regular laxative regimen. A total of 136, 21, and 82 patients received at least 1 open-label dose in studies 1, 1EXT, and 2EXT, respectively. Laxation response was also explored in this open-label setting and appeared to be maintained over the course of 3 to 4 months of open-label treatment.

Opioid Use and Pain Scores

No relationship between baseline opioid dose and laxation response in methylnaltrexone bromide-treated patients was identified in exploratory analyses of these studies. In addition, median daily opioid dose did not vary meaningfully from baseline in either RELISTOR-treated patients or in placebo-treated patients. There were no clinically relevant changes in pain scores from baseline in either the methylnaltrexone bromide or placebo-treated patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

NDC NUMBER	PACK SIZE	CONTENTS
65649-551-02	1 vial per carton	one 12 mg/0.6 mL single-use vial
65649-553-05	7 trays per kit	Each tray contains: one 12 mg/0.6 mL single-use vial, one 1 cc (mL) syringe with retractable (27-gauge x ½-inch) needle (VanishPoint®), two alcohol swabs
65649-552-04	7 pre-filled syringes per carton	seven 8 mg/0.4 mL single-use pre-filled syringes with needle guard system
65649-551-03	7 pre-filled syringes per carton	seven 12 mg/0.6 mL single-use pre-filled syringes with needle guard system
65649-551-07	1 pre-filled syringe per carton	one 12mg/0.6 mL single-use pre-filled syringe with needle guard system

16.1 Storage

RELISTOR should be stored at 20˚C to 25ºC (68˚F to 77ºF); excursions permitted to 15˚C to 30°C (59˚F to 86°F) [see USP Controlled Room Temperature]. Do not freeze. **Protect from light.**

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

- Instruct patients not to continue taking RELISTOR and to promptly notify their physician if they experience severe, persistent, or worsening abdominal symptoms because these could be symptoms of gastrointestinal perforation [*see Warnings and Precautions (5.1)*].
- Instruct patients not to continue taking RELISTOR if they experience severe or persistent diarrhea. Inform patients that common side effects of RELISTOR include abdominal pain, flatulence, nausea, dizziness, and diarrhea.
- Advise patients to be within close proximity to toilet facilities once the drug is administered.

- Instruct patients with opioid-induced constipation and advanced illness to administer one dose subcutaneously every other day, as needed, but no more frequently than one dose in a 24-hour period.

- Instruct patients to discontinue RELISTOR if they stop taking their opioid pain medication.

- Instruct patients to use the RELISTOR single-use vial with a 27 gauge x ½-inch needle and 1 mL syringe.

Patient Information

RELISTOR® (rel - *i* – *store*)
(methylnaltrexone bromide)
Subcutaneous Injection

Read this Patient Information that comes with RELISTOR before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is RELISTOR?

RELISTOR is a prescription medicine used to treat constipation that is caused by prescription pain medicines, called opioids, in patients receiving supportive care for their advanced illness, when other medicines for constipation, called laxatives, have not worked well enough.

It is not known if RELISTOR is safe and effective if used for longer than 4 months in people with advanced illness.

It is not known if RELISTOR is safe and effective in children.

Who should not use RELISTOR?

Do not use RELISTOR if you have or may have a blockage in your intestines called a mechanical bowel obstruction. Symptoms of this blockage are vomiting, stomach pain, and swelling of your stomach-area (abdomen). Talk to your healthcare provider if you have any of these symptoms before using RELISTOR.

What should I tell my healthcare provider before using RELISTOR?

Before you start using RELISTOR, tell your healthcare provider if you:

- have kidney problems
- have or had cancer of the stomach or intestine
- have or had a stomach ulcer
- have had a blockage in your intestine
- have any other medical condition
- are pregnant or plan to become pregnant. It is not known if RELISTOR can harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if RELISTOR passes into your breast milk.

Tell your healthcare provider about all medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Continue taking your other medicines for constipation unless your healthcare provider tells you to stop taking them.

How should I use RELISTOR?

- RELISTOR is injected under the skin (subcutaneous injection) of the upper arm, abdomen, or thigh.
- Inject RELISTOR exactly as your healthcare provider tells you.
- RELISTOR is usually used every other day. Do not inject more than one dose of RELISTOR in a 24-hour period.
- Stay close to a toilet after using RELISTOR.
- Stop using RELISTOR if you stop taking your prescription opioid pain medicine.
- If you inject more RELISTOR than prescribed, talk to your healthcare provider right away.

See the detailed Instructions for Use that comes with RELISTOR for information about how to prepare and inject RELISTOR, and properly throw away (dispose of) used needles and syringes the right way.

What are the possible side effects of RELISTOR?

RELISTOR can cause serious side effects, including:

- **Tear in your stomach or intestinal wall (perforation).**

  Stop using RELISTOR and call your healthcare provider right away if you develop swelling or pain in your stomach-area (abdomen) that is severe, gets worse, or that does not go away, nausea or vomiting that does not go away, or if you vomit blood or have black sticky stools.
- **Diarrhea that is severe or that will not go away.** Stop using RELISTOR and call your healthcare provider if you get diarrhea that is severe or that does not go away during treatment with RELISTOR.

The most common side effects of RELISTOR include:

- stomach-area (abdomen) pain
- gas
- nausea
- dizziness
- diarrhea
- sweating

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of RELISTOR.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store RELISTOR?

- Store RELISTOR vials and pre-filled syringes at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not freeze RELISTOR.
- Keep RELISTOR away from light until you are ready to use it.
- If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period.

Keep RELISTOR and all medicines, needles and syringes out of the reach of children.

General information about RELISTOR

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use RELISTOR for a condition for which it was not prescribed. Do not give RELISTOR to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about RELISTOR. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about RELISTOR that is written for health professionals.

For more information, go to WWW.RELISTOR.COM.

What are the ingredients in RELISTOR?

Active ingredient: methylnaltrexone bromide
Inactive ingredients: sodium chloride, edetate calcium disodium USP, glycine hydrochloride.
During manufacture, the pH may have been adjusted with hydrochloric acid and/or sodium hydroxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Salix Pharmaceuticals, Inc.
Raleigh, NC 27615

Under license from:

Progenics Pharmaceuticals, Inc.
Tarrytown, NY 10591

Revised: AUG 2013

Product protected by U.S. Patent Nos. 6,559,158, 8,247,425, and 8,420,663.

Please see www.salix.com for patent information

Instructions for Use

RELISTOR® (rel-i-store)
(methylnaltrexone bromide)

Pre-filled Syringe

Read this Instructions for Use before you start using RELISTOR and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

The following instructions explain how to prepare and give an injection of RELISTOR the right way, when using a pre-filled syringe of RELISTOR.

Important information:

- **Do not** use a RELISTOR pre-filled syringe and attached needle more than one time, even if there is medicine left in the syringe. **See Step 4 "Dispose of used pre-filled syringes and needles."**
- Safely throw away RELISTOR pre-filled syringes and attached needle after use.
- To avoid needle-stick injuries, **do not** recap used needles.
- Avoid touching the trigger fingers of the RELISTOR pre-filled syringe to keep from activating the needle guard (safety device) too soon. The needle guard is activated by pressure from the plunger on the trigger fingers (See Figure A).

Gather the supplies you will need for your injection (See Figure A). These include:

- 1 RELISTOR pre-filled syringe with attached needle
- 1 alcohol swab
- 1 cotton ball or gauze
- 1 adhesive bandage
- a container to dispose of used pre-filled syringes and needles. See Step 4: "Dispose of used pre-filled syringes and needles."

Pre-filled Syringe Parts

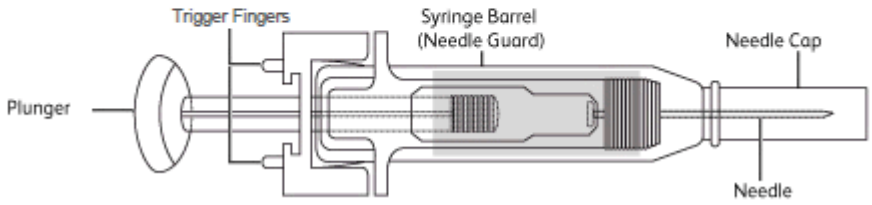


Figure A

Step 1: Choose and prepare the injection site

- Choose an injection site on your abdomen, thighs, or upper arms. See the shaded areas in Figures B and C below. Do not inject at the exact same spot each time (rotate injection sites). Do not inject into areas where the skin is tender, bruised, red or hard. Avoid areas with scars or stretch marks.

  Figure B Abdomen or thigh – use these sites when injecting yourself or another person.
  Figure C Upper arm – use this site only when injecting another person.

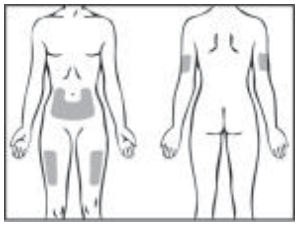


Figure B **Figure C**

- Clean the injection site with an alcohol swab and let it air dry. Do not touch this area again before giving the injection (See Figure D).

Figure D

Step 2: Prepare the pre-filled syringe

- Choose a flat, clean, well-lit work surface.
- Wash your hands with soap and water before preparing for the injection.
- Look at the pre-filled syringe of RELISTOR (See Figure E). Make sure that the dose prescribed by your healthcare provider matches the dose on the pre-filled syringe label. Look at the plunger rod of the syringe. If the dose prescribed by your healthcare provider is 8 mg, the plunger rod will be yellow; if the prescribed dose is 12 mg, the plunger rod of the syringe will be dark blue (See Figure E).

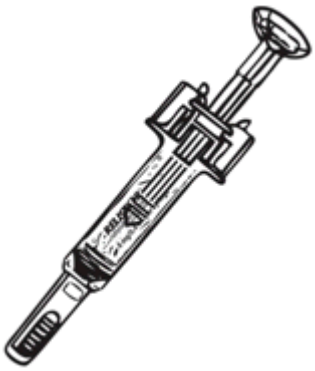


Figure E

- The liquid in the pre-filled syringe should be clear and colorless to pale yellow, and should not have any particles in it. Do not use the pre-filled syringe if it looks discolored, cloudy, or has any particles.

- Use one hand to firmly hold the barrel of the pre-filled syringe. Use your other hand to pull the needle cap straight off (Figure F). Do not touch the needle or allow it to touch anything.

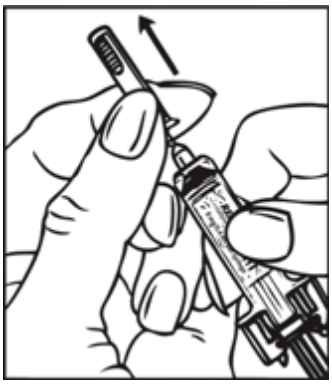


Figure F

Step 3: Inject RELISTOR

- Use one hand to pinch the skin around the injection site (See Figure G).

Figure G

- Use your other hand to hold the pre-filled syringe. Insert the full length of the needle into the skin at a 45-degree angle with a quick "dart-like" motion (See Figure H).

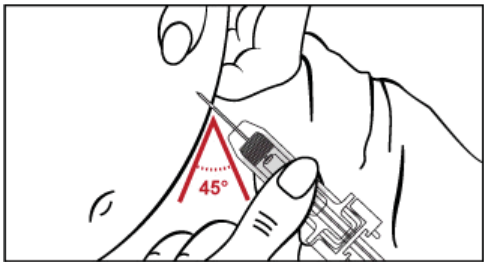


Figure H

- Let go of the skin and slowly push the plunger in with your thumb until the pre-filled syringe is empty (See Figure I). This will release the needle guard (safety device).

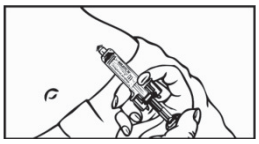


Figure I

- Continue to hold pressure on the plunger with your thumb and quickly pull the needle out of the skin. Be careful to keep the needle at the same angle as it was inserted. Remove your thumb from the plunger to allow the protective sleeve to cover the needle (See Figure J). There may be a little bleeding at the injection site.

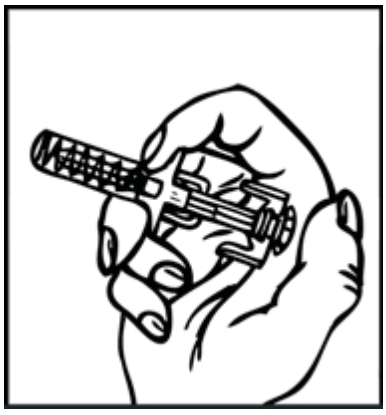


Figure J

- Hold a cotton ball or gauze over the injection site (See Figure K). Do not rub the injection site. Apply an adhesive bandage to the injection site if needed.

Figure K

Step 4: Dispose of used pre-filled syringes and needles

- **Do not** re-use the pre-filled syringe and attached needle.
- To avoid needle-stick injuries**, do not** recap used needles.
- Put your used pre-filled syringes and attached needles **in a** FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal .
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- If you have any questions, talk to your healthcare provider or pharmacist.

How should I store RELISTOR?

- Store pre-filled syringes at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not freeze RELISTOR.
- Keep RELISTOR away from light until you are ready to use it.

Keep RELISTOR and all medicines, needles and syringes out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Salix Pharmaceuticals, Inc.

Salix Pharmaceuticals, Inc.
Raleigh, NC 27615

Under license from:

Progenics®
Pharmaceuticals

Progenics Pharmaceuticals, Inc.
Tarrytown, NY 10591

Revised AUG 2013

Product protected by U.S. Patent Nos. 6,559,158, 8,247,425, and 8,420,663.

See www.salix.com for patent information

Instructions for Use

RELISTOR® (rel-i-store)
(methylnaltrexone bromide)
Vial and Syringe with Retractable Needle in Tray

Read this Instructions for Use before you start using RELISTOR and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

The following instructions explain how to prepare and give an injection of RELISTOR the right way, when using a RELISTOR tray containing a syringe with a retractable needle. A retractable needle is one that is pulled back so that it is covered after use, to prevent needle-stick injury.

Important information:

- **Do not** use a RELISTOR vial more than one time, even if there is medicine left in the vial.
- If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, carefully recap the needle and keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period. For more information about how to store RELISTOR, see the section called "**How should I store RELISTOR?**" at the end of this Instructions for Use**.**
- Safely throw away RELISTOR vials after use.
- **Do not** reuse syringes and needles. **See Step 5: "Dispose of used syringes and needles"** for information about how to safely throw away used needles and syringes.
- To avoid needle-stick injuries, **do not** recap used needles.

Your tray should include (See Figure A):

- 1 RELISTOR vial
- 1 1 mL syringe with retractable needle (VanishPoint®)
- 2 alcohol swabs

You will also need:

- 1 cotton ball or gauze
- 1 adhesive bandage
- a container to dispose of your used syringes and needles. See Step 5: "Dispose of used syringes and needles."

Vial and Syringe Parts

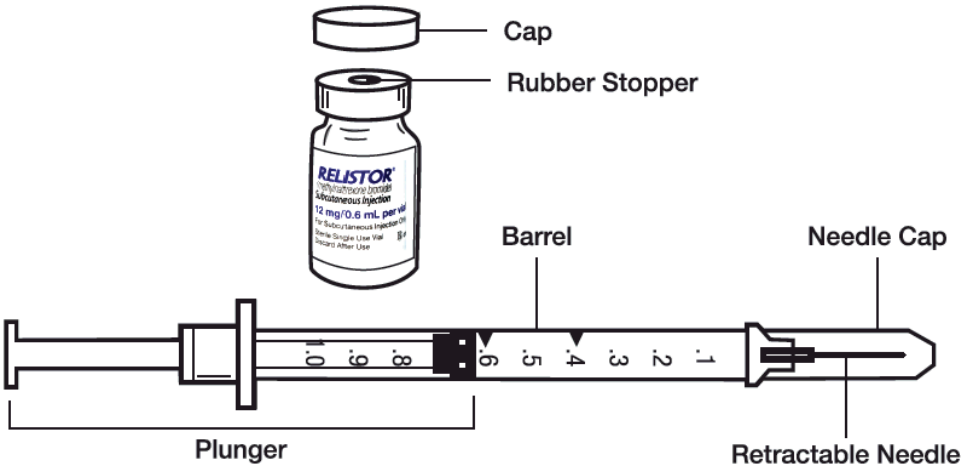


Figure A

Step 1: Choose and prepare the injection site

- Choose an injection site on your abdomen, thighs, or upper arms. See the shaded areas in B and C below. Do not inject at the exact same spot each time (rotate injection sites). Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid areas with scars or stretch marks.

  Figure B Abdomen or thigh – use these sites when injecting yourself or another person.

  Figure C Upper arm – use this site only when injecting another person.

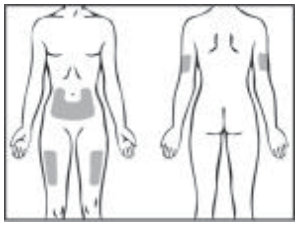


Figure B **Figure C**

- Clean the injection site with an alcohol swab and let it air dry. Do not touch this area again before giving the injection (See Figure D).

Figure D

Step 2: Prepare the injection

- Choose a flat, clean, well-lit work surface.
- Wash your hands with soap and water before preparing for the injection.
- Look at the vial of RELISTOR (See Figure E). The liquid in the vial should be clear and colorless to pale yellow, and should not have any particles in it. Do not use the vial if it looks discolored, cloudy, or has any particles.

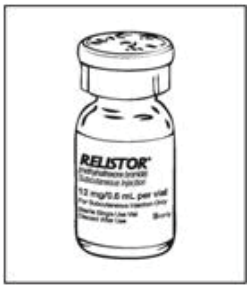


Figure E

Step 3: Prepare the syringe

- Remove the cap from the vial containing RELISTOR (See Figure F).

Figure F

- Wipe the rubber stopper with an alcohol swab (See Figure G).

Figure G

- Firmly hold the barrel of the syringe with one hand. With your other hand, pull the needle cap straight off (See Figure H). Do not touch the needle or allow it to touch anything

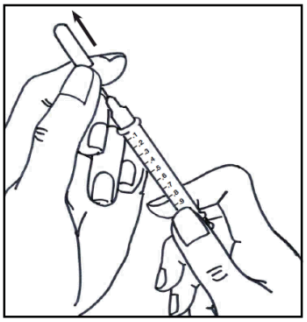


Figure H

- Carefully pull back on the plunger to the line that matches the dose prescribed by your healthcare provider (See Figures I and J). For most people, this will be the 0.4 mL mark which is an 8 mg dose or the 0.6 mL mark which is a 12 mg dose.

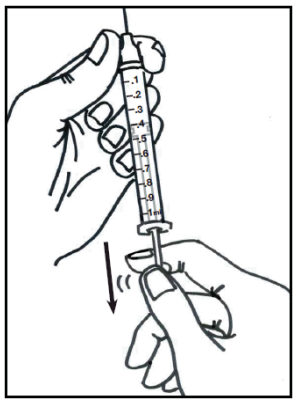


Figure I

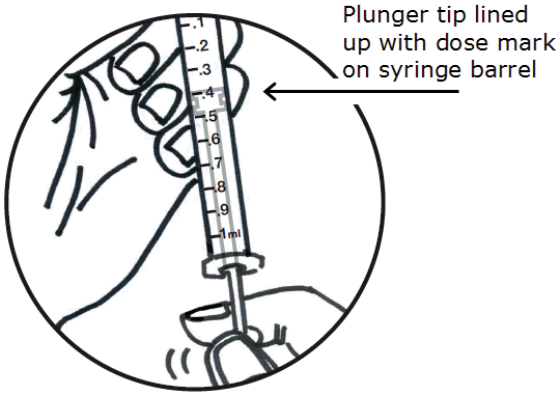


Figure J

- Use one hand to hold the vial steady. Use your other hand to insert the needle straight down into the rubber top of the RELISTOR vial (See Figure K). Do not insert it at an angle. This may cause the needle to bend or break. You will feel some resistance as the needle passes through the rubber top.

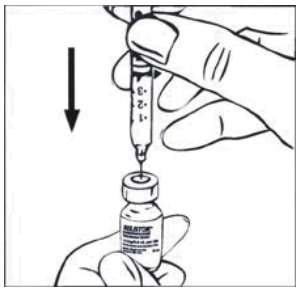


Figure K

- Gently push down on the plunger until you feel resistance, and most of the air has gone from the syringe into the vial (See Figure L). Stop pushing down on the plunger when you feel resistance. If you continue to push down on the plunger when you feel resistance, the needle will pull back (retract) into the syringe barrel.

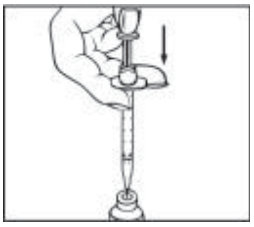


Figure L

- With the needle still in the vial, turn the vial and syringe upside down. Hold the syringe at eye level. Make sure the tip of the needle is in the fluid. Slowly pull back on the plunger (See Figure M) until the tip lines up with the mark that matches your prescribed dose. For most people, this will be the 0.4 mL mark which is an 8 mg dose or the 0.6 mL mark which is a 12 mg dose.

Figure M

- You may see some fluid or bubbles inside the vial when the syringe is filled. This is normal.

- With the needle still in the vial, gently tap the syringe to make any air bubbles rise to the top (See Figure N).

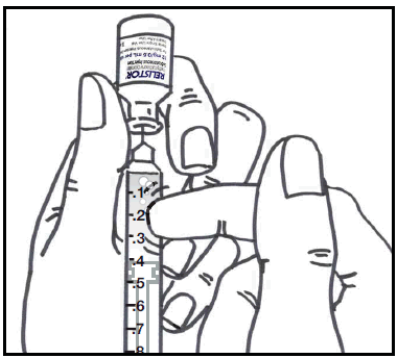


Figure N

- Gently push the plunger up until all air bubbles are out of the syringe (See Figure O). A small air bubble may stay in the syringe. This is okay and it will not affect the dose of medicine in the syringe.

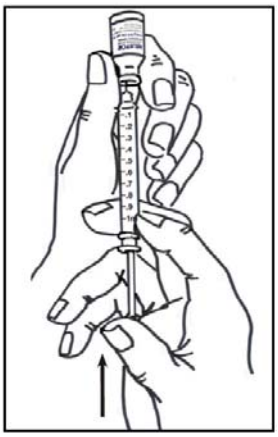


Figure O

- Make sure the tip of the needle is in the fluid. Slowly pull back the plunger to draw the right amount of liquid back into the syringe (See Figure P).

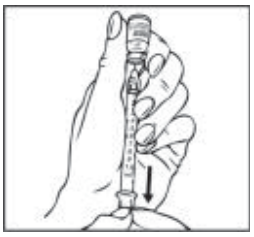


Figure P

Check to be sure that you have the right dose of RELISTOR in the syringe.

- Slowly withdraw the needle from the vial. Do not touch the needle or allow it to touch anything). Safely throw away the vial with any unused medicine.

Step 4: Inject RELISTOR

- Use one hand to pinch the skin around the injection site (See Figure Q).

Figure Q

- Use your other hand to hold the syringe. Insert the full length of the needle into the skin at a 45-degree angle with a "quick dart-like" motion (See Figure R).

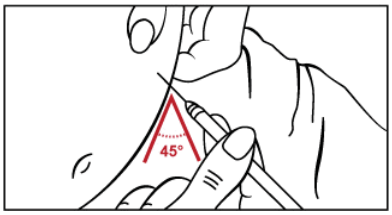


Figure R

- Let go of the skin and slowly push in on the plunger past the resistance point, until the syringe is empty and you hear a click (See Figure S).

Figure S

- The click sound means that the needle (T) has been pulled back (retracted) into the syringe barrel (See Figure U). You can now remove the syringe from your skin.

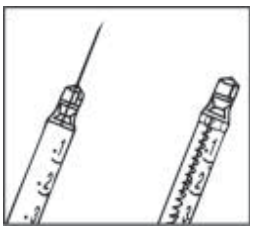


Figure T Figure U

- Hold a cotton ball or gauze over the injection site (See Figure V). Do not rub the injection site. Apply an adhesive bandage to the injection site if needed.

Figure V

Step 5: Dispose of used syringes and needles

- **Do not** re-use syringes or needles.
- To avoid needle-stick injuries, **do not** recap used needles.
- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

- If you have any questions, talk to your healthcare provider or pharmacist.

How should I store RELISTOR?

- Store RELISTOR vials at room temperature between 68°F to 77°F (20 °C to 25°C).
- Do not freeze RELISTOR.
- Keep RELISTOR away from light until you are ready to use it.
- If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period.

Keep RELISTOR and all medicines, needles and syringes out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Salix Pharmaceuticals, Inc.
Raleigh, NC 27615

Under license from:

Progenics Pharmaceuticals, Inc.
Tarrytown, NY 10591

Revised AUG 2013

Product protected by U.S. Patent Nos. 6,559,158, 8,247,425, and 8,420,663.

See www.salix.com for patent information

Instructions for Use

RELISTOR® (rel-i-store)
(methylnaltrexone bromide)
Subcutaneous Injection

Vial

Read this Instructions for Use before you start using RELISTOR and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

The following instructions explain how to prepare and give an injection of RELISTOR the right way, when using a vial of RELISTOR.

Important information:

- Use the syringes and needles prescribed by your healthcare provider.
- **Do not** use a RELISTOR vial more than one time, even if there is medicine left in the vial.
- If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, carefully recap the needle and keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period. For more information about how to store RELISTOR, see the section **"How should I store RELISTOR**?" at the end of this Instructions for Use.
- Safely throw away RELISTOR vials after use.
- **Do not** re-use syringes or needles. **See Step 5 "Dispose of used syringes and needles"** for information about how to safely throw away used needles and syringes.
- To avoid needle-stick injuries, **do not** recap used needles.

Gather the supplies you will need for your injection (See Figure A.). These include:

- 1 RELISTOR vial
- 1 1 mL syringe with a 27-gauge, ½ inch needle for subcutaneous use
- 2 alcohol swabs
- 1 cotton ball or gauze
- 1 adhesive bandage
- a container to dispose of used syringes and needles. See Step 5: "Dispose of used syringes and needles."

Vial and Syringe Parts

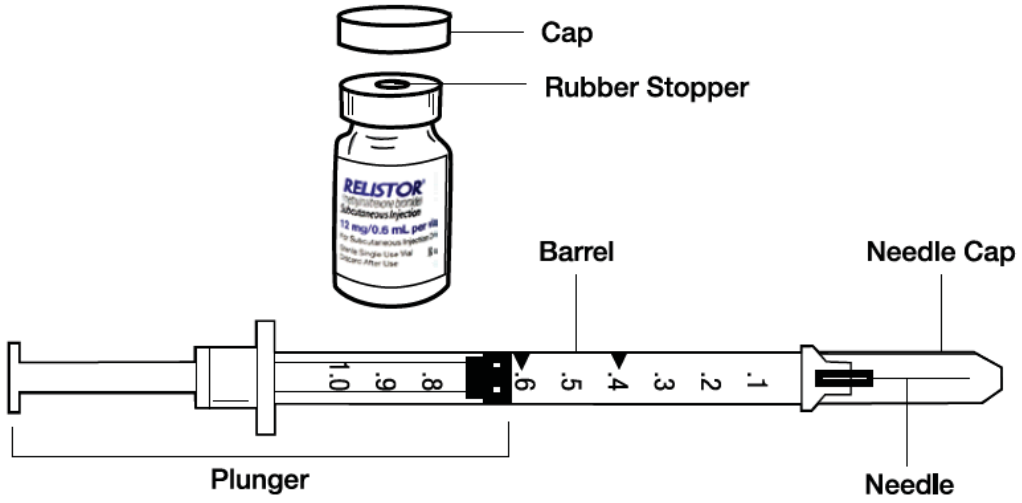


Figure A

Step 1: Choose and prepare the injection site

- Choose an injection site on your abdomen, thighs, or upper arms. See the shaded areas in Figures B and C below. Do not inject at the exact same spot each time (rotate injection sites). Do not inject into areas where the skin is tender, bruised, red or hard. Avoid areas with scars or stretch marks.

  Figure B Abdomen or thigh – use these sites when injecting yourself or another person.

  Figure C Upper arm – use this site only when injecting another person.

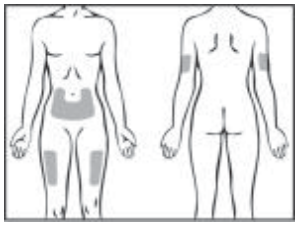


Figure B **Figure C**

- Clean the injection site with an alcohol swab and let it air dry. Do not touch this area again before giving the injection (See Figure D).

Figure D

Step 2: Prepare the injection

- Choose a flat, clean, well-lit work surface.
- Wash your hands with soap and water before preparing for the injection.
- Look at the vial of RELISTOR (See Figure E). The liquid in the vial should be clear and colorless to pale yellow, and should not have any particles in it. Do not use the vial if it looks discolored, cloudy, or has any particles.

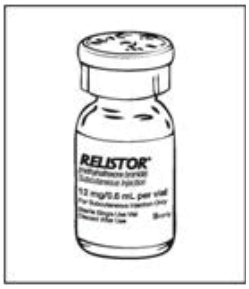


Figure E

Step 3: Prepare the syringe

- Remove the cap from the RELISTOR vial (See Figure F).

Figure F

- Wipe the rubber stopper with an alcohol swab (See Figure G).

Figure G

- Firmly hold the barrel of the syringe with one hand. With your other hand, pull the needle cap straight off (See Figure H). Do not touch the needle or allow it to touch anything.

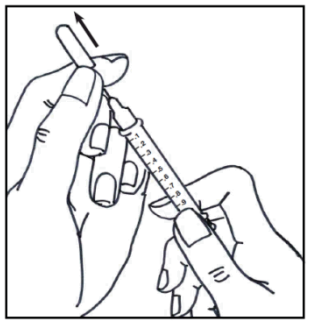


Figure H

- Carefully pull back on the plunger to the line that matches the dose prescribed by your healthcare provider (See Figures I and J). For most people, this will be the 0.4 mL mark which is an 8 mg dose or the 0.6 mL mark which is a 12 mg dose.

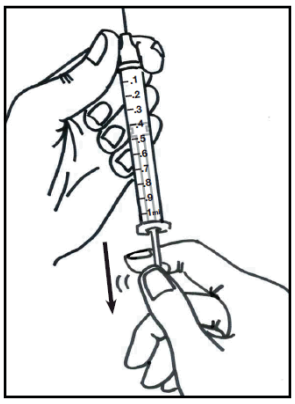


Figure I

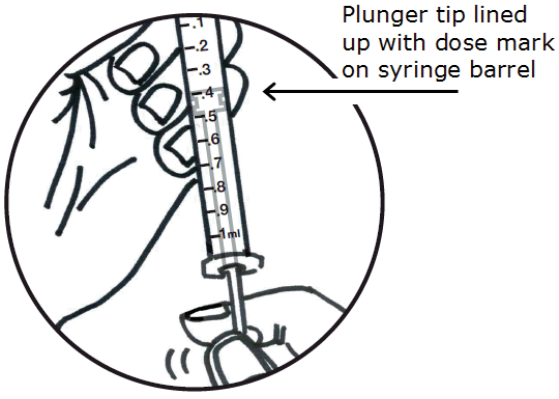


Figure J

- Use one hand to hold the vial steady. Use your other hand to insert the needle straight down into the rubber top of the vial (See Figure K). Do not insert it at an angle. This may cause the needle to bend or

break. You will feel some resistance as the needle passes through the rubber top.

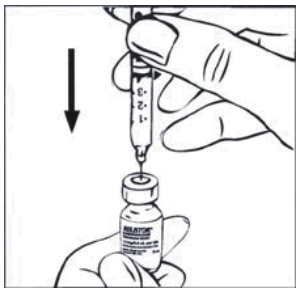


Figure K

- Gently push down the plunger until all of the air has gone from the syringe into the vial (See Figure L).

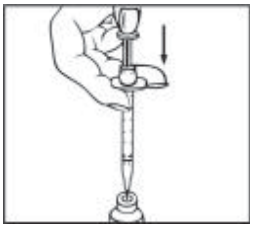


Figure L

- With the needle still in the vial, turn the vial and syringe upside down. Hold the syringe at eye level. Make sure the tip of the needle is in the fluid. Slowly pull back on the plunger (See Figure M) until the tip lines up with the mark that matches your prescribed dose. For most people, this will be the 0.4 mL mark which is an 8 mg dose or the 0.6 mL mark which is a 12 mg dose.

Figure M

- You may see some fluid or bubbles inside the vial when the syringe is filled. This is normal.

- With the needle still in the vial, gently tap the side of the syringe to make any air bubbles rise to the top (See Figure N).

Figure N

- Slowly push the plunger up until all air bubbles are out of the syringe (See Figure O). A small air bubble may stay in the syringe. This is okay and it will not affect the dose of medicine in the syringe.

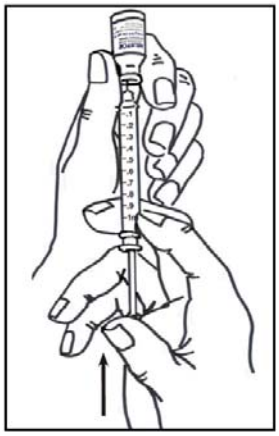


Figure O

- Make sure the tip of the needle is in the fluid. Slowly pull back the plunger to draw the right amount of liquid back into the syringe (See Figure P).

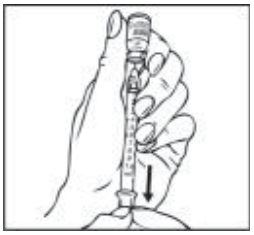


Figure P

Check to be sure that you have the right dose of RELISTOR in the syringe.

- Slowly withdraw the needle from the vial. Do not touch the needle or allow it to touch anything. Safely throw away the vial with any unused medicine.

Step 4: Inject RELISTOR

- Use one hand to pinch the skin around the injection site (See Figure Q).

Figure Q

- Use your other hand to hold the syringe. Insert the full length of the needle into the skin at a 45-degree angle with a quick "dart-like" motion (See Figure R).

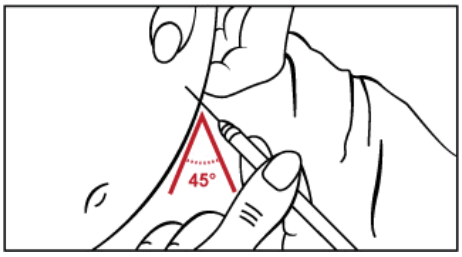


Figure R

- Let go of the skin and slowly push in on the plunger until the syringe is empty (Figure S).

Figure S

- When the syringe is empty, quickly pull the needle out of the skin, being careful to keep it at the same angle as it was inserted. There may be a little bleeding at the injection site.

- Hold a cotton ball or gauze over the injection site (Figure T). Do not rub the injection site. Apply an adhesive bandage to the injection site if needed.

Figure T

Step 5: Dispose of used syringes and needles

- **Do not** re-use a syringe or needle.
- To avoid needle-stick injuries, **do not** recap a used needle.
- Put your used needles and syringes in a FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic,
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
  - upright and stable during use,
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.
- If you have any questions, talk to your healthcare provider or pharmacist.

How should I store RELISTOR?

- Store RELISTOR vials at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not freeze RELISTOR.
- Keep RELISTOR away from light until you are ready to use it.
- If RELISTOR has been drawn into a syringe and you are unable to use the medicine right away, keep the syringe at room temperature for up to 24 hours. The syringe does not need to be kept away from light during the 24-hour period.

Keep RELISTOR and all medicines, needles and syringes out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Salix Pharmaceuticals, Inc.
Raleigh, NC 27615

Under license from:

Progenics Pharmaceuticals, Inc.
Tarrytown, NY 10591

Revised AUG 2013

Product protected by U.S. Patent Nos. 6,559,158, 8,247,425, and 8,420,663.

See www.salix.com for patent information

10.2 Summary of Unadjudicated MACE in Studies 3356 and 3358

Table 32 presents a summary listing of all 7 unadjudicated MACE cases. The table includes CV history and risk factors, adjudication assessment, and notes for each patient. Patients are listed as Subjects A through G in this table, as they are identified in Table 19 in the body of the document.

Table 32: Summary of Unadjudicated MACE in Study 3358 with CV Risk Factors and Adjudication Assessment

Patient ID/ Event Term	Age & Sex	Opioids (METDD)	Pertinent Medical History / CV Risk Factors	Doses Prior to SAE(Days Off Drug at SAE)	Adjudication Assessment and Patient Notes
Subject A **MI** (Non-fatal)	57 F	Oxycodone (80 mg)	BMI= 23, CAD, hyperlipidemia, smoker, COPD	291 (2)	Well-documented MI in patient with high CV risk. • Normal ECG at Screening • No BP/HR changes during study • After stent placement, completed study with no other issues.
Subject B **MI** (Non-fatal)	59 M	Methadone (1125 mg)	BMI= 33, CAD, smoker, uncontrolled hypertension, dyslipidemia, hyperglycemia, family history of MI	6 (0)	MI diagnosed on post-event imaging and symptom recall. • MI resolved on study treatment with no recurrence. • Underwent coronary artery bypass graft surgery and maintained on Relistor through Study Day 274; discontinued due to relocation (moved)
Subject C **Presumed MI (CV Death)**	57 M	Hydro-morphone/ Fentanyl (224 mg)	BMI= 29, angina, CAD, dyslipidemia, previous MI (stent placements), smoker, hypertension	248 (13)	CV death in high risk patient with CAD. No evidence of MI. • Found dead at home on Study Day 278 (13 days after last dose) • No autopsy.
Subject D **Small Bowel Obstruction, MI** (Non-fatal)	81 F	Morphine (180 mg)	BMI=32. angina, hyperlipidemia, carotid endarectromy, CVA	140 (5)	No evidence of MI, likely complication of small bowel obstruction • Event occurred 5 days after SBO, presumably from previous cholecystectomy. After stent placement patient resumed Relistor and completed study. • Troponins 0.07 and 0.1 (12 hrs later). • T wave inversion in central pre-cordial leads.

Table 32: Summary of Unadjudicated MACE in Study 3358 with CV Risk Factors and Adjudication Assessment (Cont'd)

Patient ID/ Event Term	Age & Sex	Opioids (METDD)	Pertinent Medical History / CV Risk Factors	Doses Prior to SAE(Days Off Drug at SAE)	Adjudication Assessment and Patient Notes
Subject E **CVA** (Fatal) No autopsy	45 F	Oxycodone *(no pain meds for 11d prior to event)*	BMI = 46, poorly controlled hypertension, sinus bradycardia	210 (0)	No evidence of CVA. • Potential etiologies include drug abuse, arrhythmia, or cardiomyopathy.
Subject F **Cardiac arrest** (Fatal) No autopsy.	68 F	Codeine *(no pain meds for 5d prior to event)*	BMI = 47, hypertension, history of tobacco use and paroxysmal supraventricular tachycardia	57 (6)	Sudden death of unknown etiology. • Spent night in car in moribund state after a visit to urgent care for pain meds (out of pain meds for 5 days). Found unresponsive next morning.
Subject G **Sudden Death** Autopsy results unavailable	46 M	Morphine Oxycodone (320 mg)	BMI = 24, ALS, seizures, low oxygen saturation, asthma, smoker	238 (7)	Patient likely died of ALS.

Abbreviations: CV = cardiovascular; BMI = body mass index; y/o = year old; MACE = major adverse cardiac event; ALS = amyotrophic lateral sclerosis; SBO = small bowel obstruction COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; CAD = coronary artery disease; MI = myocardial infarction; CVA = cerebrovascular accident; and CHF = congestive heart failure.

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